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FEATURES

THE CHICAGO MEDICAL SCHOOL
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TOWARD AN UNDERSTANDING OF THE THYROID

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The proper management of thyroid disease is dependent upon a thorough understanding of the physiology of the thyroid gland and its strategic position in the endocrine system. The thyroid-pituitary axis lends itself well as an example of an endocrinological axiom, viz.,

"Removal (or destruction) of an endocrine gland which makes a tropic hormone causes atrophy of the gland upon which that hormone acts. Also, removal of an endocrine gland for which another gland makes a tropic hormone causes hyperactivity of the latter gland."[1]

The thyroid gland is under the direct control of the pituitary as mediated through release of thyroid stimulating hormone (TSH). In a normal (euthyroid) individual, the secretion of TSH is, in part, regulated by the level of thyroid hormone in the blood, thus setting up a homeostatic mechanism. Removal of the anterior lobe of the pituitary results in atrophy of the thyroid gland. TSH has three important effects upon the thyroid gland:

1. It increases the uptake of ingested iodide from the blood stream into the thyroid gland;
2. It increases the formation of the storage form of thyroid hormone (thyroglobulin);
3. It accelerates release of thyroid hormone (e.g., thyroxine) into the blood stream.

The causes of hyperthyroidism are not known. One of the theories holds that repeated physiological and emotional stress are mediated through the hypothalamus to the pituitary, increasing output of TSH. In another theory, the thyroid gland is said to become hypersensitive to the usual amounts of TSH.

The etiology of hypothyroidism, which in an advanced form is myxedema, is:

1. surgical removal of the thyroid gland (most common cause);
2. spontaneous atrophy of the thyroid gland—cause unknown;
3. prolonged use of anti-thyroid drugs;
4. pituitary disease
   (a) decreased output of TSH;
   (b) postpartum hemorrhagic infarction of the pituitary (Sheehan-Murdock syndrome);
   (c) Simmonds' disease;
   (d) destructive neoplasm of the pituitary or the surrounding area;
   (e) cranio-pharyngiomas.

RELATION OF IODINE TO THE THYROID GLAND

Our requirements of iodine are minute —25 gamma per day. The average diet, especially if iodized salt is used, supplies far more than this amount. Thus, iodine supplements are usually not necessary. It should be mentioned that in certain sections of the country such as the Great Lakes region and upper Mississippi Valley, the average diet may not contain even the minimum requirements of iodine, as a result of which thyroid disturbance is more common and additional

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iodine in the form of iodized salt should be taken. It is probable that insufficient iodine in the diet plus goitrogenic foods may cause goiter. Iodine lack alone, in the absence of goitrogens, will not yield goiter; but if sufficient goitrogens are ingested, goiter may develop despite adequate iodine intake.

Ingested iodine, usually in the form of iodide, is absorbed from the gastrointestinal tract and picked up by the thyroid gland, which converts the iodide $[I]^-$ to elemental iodine (I_2). This combines with the amino acid tyrosine to form di-iodotyrosine, 2 molecules of which form thyroxine. Thyroxine is then bound to a globulin and stored as thyroglobulin.

Iodine can also be absorbed through the skin and respiratory tree. The iodine which is not stored or utilized by the body is excreted almost entirely in an inorganic state, principally by the kidney. Some iodine is also excreted in the urine, bile, skin, lungs, milk and saliva.

The thyroid cell is unique in that it is the only cell that forms a hormone, secretes it into a follicle for storage, and then, upon demand, frees the hormone from its globulin storage partner and releases it into the blood. In the blood it is bound to albumin and is known as protein-bound or organic iodine and constitutes 70% of the total serum iodine.

ACTION OF ANTI-THYROID DRUGS

In thyrotoxicosis three groups of drugs are effective therapeutic measures:

A. *Iodine.* Iodine has 3 general effects, the first 2 of which counteract or overweigh the third.
   (1) It inhibits the action of TSH by altering the chemical structure of one of its attached groups (converts active SR radical to less active SS).
   (2) It inhibits the proteolytic enzymatic reaction whereby the colloid storage thyroglobulin is mobilized and released as thyroxine.
   (3) Being an integral component of thyroglobulin, iodine augments its formation.

These effects of iodine are more qualitative than quantitative and are equally effective in all forms of iodine administration. Thus, 6 minims of Lugol's solution a day are as effective as many times that dose.

B. *Cyanates.* The anti-thyroid or goitrogenic effect of cyanates was discovered accidentally during the course of treatment of hypertension by the administration of thiocyanates. It was noted that many hypertensive patients thus treated developed swelling of the thyroid gland with evidence of decreased thyroid function, thereby producing a paradoxical situation wherein a gland is enlarged while its release of active hormone is actually reduced. The mode of action of cyanates is said to be:
   (1) the interference with the actual uptake and retention of iodide by the thyroid gland, thus reducing the formation and ultimate release of thyroid hormone; and
   (2) the goitrogenic results produced by the enhancement of TSH.

Therefore, although the gland may be activated by TSH, the "blocking" effect of cyanates upon iodide uptake actually reduces the ultimate formation of thyroid hormone.

C. *Thiourea or Thiouracil.* Thiourea or thiouracil and their numerous related substances are similarly anti-thyroid and goitrogenic, but their mode of action is slightly different. These drugs definitely augment the action of TSH, thus producing some swelling of the gland; but their action on iodine metabolism is one of interference with the *conversion* within the gland of iodide $[I]^-$ to elemental iodine (I_2).

According to Means,[1] the mechanism of the goitrogenic effect of these drugs is the same as occurs under the condition of absolute iodine deficiency. That is, applying the previously mentioned axiom, absolute lack of iodine —› decrease of circulating thyroid hormone —› stimulation of the anterior pituitary to thyrotropic activity —› increased release of TSH —› hyperplasia of the thyroid. The hyperplasia of the thyroid does not necessarily lead to an increase in the release of thyroid hormone, because of the blocking effect of the anti-thyroid drugs. The term "frustrated hyperplasia"

has been applied to this situation.

A curious parallel exists between the discovery and development of sulfonamides and the anti-thyroid drugs. Both were discovered accidentally and in each instance, the earlier derivatives had numerous untoward effects, and large dosages were required. Progress in each field led to the development of more potent forms with progressively fewer toxic effects. Although the development of new sufonamides was halted by the more effective biological antibiotics, the development of newer anti-thyroid drugs is still advancing. Table I illustrates the development of these drugs. Certainly, more effective, less toxic anti-thyroid drugs can be anticipated.

PHYSIOLOGICAL EFFECTS OF THE THYROID HORMONE

A. *Calorigenic effects.*

The dramatic manifestations of the calorigenic effects of thyroid hormone have overshadowed other significant activities of the thyroid hormone. This can be demonstrated by the fact that drugs such as dinitrophenol have similar calorigenic activity, but cannot be used as a substitute for thyroid hormone and do not produce the metabolic alterations of thyrotoxicosis. The symptoms of hypermetabolism resulting from the calorigenic action, such as emotional instability, tachycardia, warm, moist skin, diarrhea, bulimia, heat sensitivity and tolerance of cold, are well-known.

B. *Effects on Water, Electrolytes, and Protein.*

An individual, when deprived of thyroid hormone, has a tendency to deposit large amounts of a peculiar albumin-like protein, together with water, in the subcutaneous and areolar tissues of the body. This protein, which is clear and viscoid, can be seen in its pure state by aspirating the distended lower lids of patients with severe myxedema. Recent studies have indicated that this material is high in hyaluronic acid content.

Deposits of this protein may be found within the skin over the anterior tibia in a peculiar, rare condition known as localized myxedema, which, paradoxically, occurs with long-standing exophthalmic goiter.

A patient with generalized myxedema is actually afflicted with "proteinous dropsy." This material augments the osmotic forces of the interstitial tissues and may be a factor in the reduced blood volume of myxedema. The deposit of water within this "gel" binds with it electrolytes. Hence, the administration of thyroid to such an individual results in breakdown of this "proteinous gel" and causes a diuresis of water and electrolytes. It is not unusual for the patient with myxedema to lose 10-15 pounds during the first few weeks of thyroid administration.

C. *Effects on Central Nervous System.*

The effects of excess thyroid hormone on the central nervous system are so well-known that the adjective "hyperthyroid" has common usage in the English literature. This action is based on one of the fundamental properties of thyroid hormone, viz., its ability to increase activity and irritability of living cells. The familiar symptoms resulting from this property such as nervousness, emotional instability, excess motor activity, etc. need not be described in detail here.

An individual deprived of thyroid hormone becomes a study in emotional compatibility, because he is living within the lower levels of the emotional scale. He is usually an apathetic individual, whom it is almost impossible to antagonize.

D. *Effects on Muscular System*

The effects of thyrotoxicosis on muscle strength are extremely varied, ranging from mild weakness to the asthenia simulating myasthenia gravis. This peculiar aberration in muscle metabolism brings about the increased urinary excretion of creatine that has led to the development of various creatine tolerance and excretion tests. The extra-ocular muscles are notoriously susceptible to the myopathies of thyroid intoxication. The relationship of thyrotoxicosis to myasthenia gravis, although widely investigated, still remains an unsettled problem.

The exophthalmos of Grave's disease has been explained as due to the weakness and degeneration of the extra-ocular muscles, plus an actual edema, congestion, and cellular infiltration of the retro-

bulbar tissues. This latter effect is said to be due to the action of TSH and may be the explanation for the progressive exophthalmos which may develop following removal of the thyroid gland. Thomas[2] states, "Everything points, therefore, to an excess of noninactivated thyrotropin as a necessary feature of endocrine exophthalmos; and in those cases in which thyrotropin is secreted by the pituitary in large amounts, removal of the thyroid gland with its power to neutralize thyrotropin leads to the production or increase of already present exophthalmos". Theoretically, the administration of thyroid hormone should, but frequently does not, inhibit this response.

E. *Effects on Vitamin Metabolism.*

Large doses of Vitamin A also have anti-thyroid action which is poorly understood and may block the action of TSH. The peculiar lemon-colored pallor of the myxedema patient, which produces a striking clinical similarity to Addisonian anemia, is due to the inability of individuals deficient in thyroid to convert carotene to Vitamin A, thereby resulting in an accumulation of carotene within the skin and subcutaneous tissues. Deposition of the embryonal myxedema muco-protein contributes to this appearance.

Since thiamine is eminently concerned in cellular catabolism, the tremendous utilization of carbohydrate by the cells has a tendency to exhaust the stores of this vitamin. Thus, in the treatment of thyrotoxicosis, the dietary quantities of thiamine must be supplemented. A similar situation exists with the metabolism of Vitamin C.

F. *Effects on Bone Marrow.*

As previously mentioned, thyroid deficient patients may, at times, bear a striking resemblance to pernicious anemia[3] patients to the extent even of the blood picture, achlorhydria, and neurological changes and the specific response to liver extract. The exact effects on the marrow have not been thoroughly studied and bear further investigation. The dramatic response of these patients to thyroid presents the astute clinician with unusual opportunities to effect a spectacular cure.

G. *Effects on Carbohydrate Metabolism.*

Thyroid hormone has definite, easily demonstrable effects on carbohydrate metabolism. In the experimental animal administration of thyroxine depletes liver and muscle glycogen and causes gluconeogenesis with the production of carbohydrate from non-carbohydrate precursors, thus resulting in hyperglycemia.

The diabetogenic effect of thyroid hormone has been frequently demonstrated.[4] Latent diabetes in a myxedema or hypothyroid patient may manifest itself clinically upon administration of thyroid hormone. Removal or inhibition of the thyroid gland will ameliorate diabetes, and conversely, a mild diabetic may become uncontrolled with the onset of thyrotoxicosis. The mechanism of this action of thyroid hormone is not understood. Not all patients with hyperthyroidism develop diabetes or glycosuria. It may be that only those individuals with a poor pancreatic reserve will develop diabetes with the onset of hyperthyroidism. It may also be a matter of exhaustion of the beta cells of the pancreas from the enhanced demand for insulin by hyperfunctional cells utilizing large quantities of carbohydrate.

H. *Effects on Lipid Metabolism.*

We know only the effects of thyroid hormone on lipid metabolism, but the basic mechanisms involved remain unrevealed. A consistent finding in thyroid deficiency is an elevation of both the total cholesterol and cholesterol esters.[5] The phospho-lipids also have a tendency to increase in hypothyroidism. Cholesterol in hyperthyroidism is not consistently depressed and thus has limited diagnostic value in this condition.

I. *Effects on the Gonads.*

That disturbances of gonadal function are frequently associated with thyroid dysfunction is unquestioned, but one of the major problems that intrigue the students of this field is whether gonadal dysfunction is due to a decrease in thyroid hormone alone, or to a concomitant decrease in TSH and gonadotrophic hormone. It should be mentioned here that many endocrinologists believe that specific trophic hormones of the pituitary are actually chemical artefacts despite their apparent specificity in animal ex-

perimentation, and that actually only one trophic hormone is released by the anterior lobe. The specificity, therefore, would be determined by the target organ and not by the pituitary.

It is conceivable that the effects of thyroid hormone on the gonads may be, in part, nonspecific due to the increased metabolic activity induced by the hormone. Clinically, a number of gonadal aberrations may be seen in thyroid disease. Paradoxically, in thyrotoxicosis there is frequently scant or absent menstruation, while in myxedema, which develops prior to the menopause, menorrhagia may be observed. Correction of these thyroid disturbances often restores the normal menstrual cycle. Both hypo- and hyperthyroidism may be factors in male and female sterility. Therefore, small doses of thyroid have been administered empirically to both the husband and wife in certain sterility problems. In the cretin and in juvenile myxedema, the development of the genitalia is retarded and secondary sex characteristics fail to develop. In general, it may be said that the exact relationship of the thyroid gland to the sexual functions is obscure and most of our therapy in this field is empirical.

J. *Effects on Growth and Development.*

As a result of the general metabolic depression, all of the structures of the body grow more slowly when deprived of thyroid hormone. This is especially true of the skin, hair, nails and bones. Thus, the cretin or juvenile myxedema patient is unable to attain adult dimension and form. There is delayed epiphyseal union and dentition. The skin of the myxedema patient is unusually cold, dry and scaly. The hair is coarse, brittle, dry and sparse. The thinness of the hair is especially prominent over the anterior aspects of the forehead even in females. The lateral aspects of the eyebrows are thin. Means[1] and others[6] suggest that pituitary myxedema can be differentiated from spontaneous myxedema by the typical cachexia, amenorrhea, lack of axillary and pubic hair, and failure to respond to thyroid, in the pituitary type; whereas the spontaneous myxedema patient may have menorrhagia, gain weight, have normal axillary and pubic hair, and will respond dramatically to thyroid extract. We have been unable to confirm this observation for in most of our cases of myxedema (spontaneous or surgical), there was absence of axillary hair and scant pubic hair.

K. *Effect on the Cardiovascular System.*

The existence of myxedema heart disease as a clinical entity has been widely disputed. It is well-known that myxedema patients have a tendency to develop coronary disease, perhaps in association with the concomitant elevation in cholesterol and other lipids. This fact becomes painfully evident on the occasion when overly rapid administration of large doses of thyroid produces angina pectoris or even precipitates myocardial infarction.

Several cases of myxedema with massive pericardial effusions and ascites which were reversed by the administration of thyroid appear in the literature.[7] It is conceivable that those cases of cardiac enlargement attributed to myxedema, which reverted to normal size on treatment, were effusions rather than actual cardiac hypertrophy or dilatation. Means[1] states that he has not seen gross cardiac decompensation in myxedema except when other organic heart disease was present as a complication. This is in keeping with our experience.

One hears frequent references to the term "thyrocardiac" and thyrotoxicosis is often mentioned as one of the causes of heart disease. It has been questioned whether the cardiac abnormalities occasionally seen in thyrotoxicosis are due to a specific toxic effect of thyroid hormone on the myocardium or to cardiac exhaustion resulting from the overwhelming demands placed upon the heart by the elevated metabolism. Dearing[8] has described specific myocardial lesions produced in the experimental animal by the simultaneous administration of digitalis and thyroid hormone. Andrus[9] has concluded from clinical and experimental studies that thyroid hormone is not specifically toxic to the myocardium, and the deleterious effects of thyrotoxicosis on the heart are due to the increased demands. It is probable that thyrotoxicosis

exaggerates pre-existent heart disease or makes manifest latent heart disease that might go unrecognized otherwise.

It is not sufficient to make a diagnosis of cardiac decompensation without a consideration of possible etiologic factors other than mechanical deformities of the cardiac musculature or valves. Among these factors, possible thyrotoxicosis is of prime consideration. Therefore, in recurrent paroxysmal arrhythmias, in patients with congestive failure in whom the usual therapeutic measures fail to produce the desired effects, in persistent tachycardias, and in rapid ventricular rates with auricular fibrillation unresponsive to digitalis, thyrotoxicosis should be considered as an etiologic factor. Under these circumstances a therapeutic test with an iodine preparation may have dramatic results. The failure of adequate doses of digitalis to reduce measurably the apical rate should focus attention on a possible toxic thyroid.

MISCELLANEOUS AFFECTIONS OF THE THYROID GLAND

Both clinicians and pathologists have contributed to the confusion that exists in the consideration of various types of "Struma" and inflammations of the thyroid gland. A detailed description of this subject is not within the scope of this paper. Riedel Struma or Struma fibrosa is a unilateral, fibrosing, adherent tumefaction of the thyroid which is frequently considered to be carcinomatous until proven otherwise by histologic study. Although surgical removal of this diseased gland is difficult because of the fibrotic adhesions to the adjacent neck structures, it is the only satisfactory method of treatment. Hashimoto Struma or Struma lymphomatosa is an entirely separate condition which preoperatively, is seldom diagnosed correctly, except by the use of the Silverman biopsy needle.[10] This condition is characterized by the firm, bilateral irregular enlargement of the thyroid, by normal or low BMR, and by its occurrence in middle-aged women. The histologic appearance is diagnostic, and surgery followed by x-ray therapy is the treatment of choice.

Acute thyroiditis, the etiology of which is unknown, has a rather characteristic clinical picture. The onset is usually sudden with unilateral pain and swelling of the thyroid, fever, frequently chills, exquisite tenderness over the involved lobe, and pain on swallowing. The objective findings are those of a localized cellulitis. The treatment of choice again is x-ray therapy. Anti-thyroid drugs of the thyroid group have been also used with some success in this condition. Occasionally, when the course of this illness is milder, it is considered to be a subacute thyroiditis. The treatment is the same as for acute thyroiditis. There is usually no residual disturbance of thyroid function when the thyroiditis subsides. It should be mentioned that subacute thyroiditis and the Strumas are separate entities which do not progress from one to the other. Crile,[10] as a result of experience with over 100 Silverman needle biopsies, recommends this procedure highly when the diagnosis is in doubt. Needle biopsy is, of course, contraindicated when carcinoma of the thyroid is considered because of the possibility of dissemination of carcinoma by this procedure.

THE PRESENT STATUS OF RADIOACTIVE IODINE

Since radioactive iodine is now just beyond the experimental stage, its exact position in our therapeutic armamentarium is yet to be established. A consideration of this subject should be divided into two headings: 1. *Diagnosis, using minute tracer doses,* and 2. *Therapy.*

The use of radioactive iodine in diagnosis and treatment of thyroid disease is based upon the convenient affinity of the thyroid tissue for iodine. Before proceeding to a discussion of the procedures involved, a few definitions should be stated.

A commonly used unit is *r.e.p.*—roentgen equivalent physical—which is the amount of tissue ionization equivalent to that produced by one x-ray roentgen unit. *E.H.L.*—Effective Half Life—is the number of days required for the I^{131} within the gland to decrease to ½ its maximum irradiation, and is, therefore, dependent upon 2 factors:

1. the rate of physical decay of the isotope;

2. the rate at which the thyroid gland secretes or disposes of the I^{131}.

The isotope is administered in microcurie doses. One microcurie would deliver 160 r.e.p. to one gram of thyroid tissue during its entire period of radiation decay if all of this I^{131} would remain within the gland. Therefore, in order to calculate the satisfactory therapeutic doses of I^{131}, the following factors should be known:

1. the percentage of injected I^{131} that is picked up by the thyroid gland (iodine uptake);
2. the approximate weight in grams of the thyroid gland (the factor which can least accurately be determined);
3. the Effective Half Life.[11]

The use of radioactive iodine in diagnosis is based upon data collected since the beginning of this work in 1940,[12] which indicates that the thyroid of a normal individual will take up 20 to 30 per cent of injected I^{131}, the thyroid gland of a hypothyroid individual will take up less than 10 per cent, and the gland of a thyrotoxic subject will take up more than 35 per cent.[13]

It should be noted that there is considerable overlap (30 to 40 per cent) and, therefore, borderline values are of little significance. It should be mentioned that there are a great many sources of error in the use of this procedure for diagnosis, e.g., previously ingested iodine, absorption of iodine through the skin where it may have been applied as an antiseptic, and iodized substances used in diagnostic roentgenology, such as lipiodol. However, Jaffe and Ottoman[13] report the radioiodine tracer test is 95% accurate and the complete iodine test is 80% accurate; whereas the BMR is only 67% accurate. They reported no false high radioiodine uptakes in patients with other evidence of thyrotoxicosis and therefore advised radioiodine uptake tests for all patients with clinically suspect hyperthyroidism regardless of the type of treatment to be used.

In addition to measuring the 24-hour pickup of I^{131} by the use of a Geiger counter, the problem has been attacked by measuring the 24-hour urinary output of I^{131}, the plasma I^{131}, the protein-bound fraction of I^{131}, and the ratio of protein I^{131} to total I^{131} in the plasma. The direct measurement of iodine uptake by the gland and the 24-hour urinary excretion of I^{131} appear to be the most reliable procedures. They are still in the experimental stages. The radioactive iodine uptake is of definite value in diagnosis of borderline thyrotoxicosis due to diffuse hypyerplasia of the gland, and especially in the differentiation of acute and subacute thyroiditis with hypermetabolism from diffuse hyperplastic thyrotoxicosis. In the former the uptake would be decreased below normal, and in the latter the uptake would be increased. The uptake of I^{131} is of questionable value in toxic adenomas for the obvious reason that the adenoma is usually not sufficiently large nor is its avidity for iodine sufficient to increase the uptake.

Although the use of radioactive iodine as a therapeutic agent in thyrotoxicosis is an excellent tool, the inability to accurately estimate the proper dosage that will produce a remission of symptoms without resulting in a severe myxedematous state constitutes a hazard. In some clinics the weight of the gland is computed individually by three examiners and the arithmetical average constitutes the estimated weight of the gland. The margin of error inherent in so gross a method is obvious. Burrows and Ross[11] have indicated that 7,000-10,000 r.e.p. is an adequate single dose for most patients with hyperthyroidism. Other workers in this field give several smaller doses and estimate the total dosage by the clinical response of the patient.

The isotope of iodine has been widely publicized and dramatized as a cure for carcinoma of the thyroid. Actually, the enthusiasm is not justified, for a relatively small proportion of these neoplasms respond to such therapy. Of the 14 patients with carcinoma of the thyroid studied at the Sloan-Kettering Institute,[14] it was desirable and possible to administer radioactive iodine to only 20, and of these 20, objective improvement was observed in only 10. The major obstacle to the use of I^{131} in thyroid carcinoma is the lack of natural avidity for I^{131} of most of these tumors. Another

hazard is the well-known damaging effects of radiation from I^{131} on vital body tissues.[15] The previous administration of ordinary iodine-containing drugs reduces the avidity of these tumors. Frequently, the normal thyroid tissue will pick up the I^{131}, whereas the carcinomatous tissue, including the metastases, will not attract the isotope. The implications of this situation are self-evident. It may be necessary under these circumstances to surgically ablate the normal thyroid issue and increase avidity of the thyroid carcinoma for I^{131} by the administration of goitrogenic drugs (thiourea derivatives) prior to the administration of the isotope. The ideal treatment for thyroid carcinoma is still surgical removal as soon as the diagnosis is suspected.

With the dramatic advances in diagnosis and therapy of thyroid disease in the last ten years, an understanding of the recent concepts of thyroid physiology is necessary in order to better apply these newer therapeutic measures, the details of which are not within the scope of this paper. It is hoped that the material presented in this paper will in some small measure clarify an all too confusing subject.

TABLE I.[16]

ANTITHYROID DRUGS

	Dosage (mg.)	Incidence of reactions (per cent)
Thiouracil	600	10
Thiourea	200-300	16
Thiobarbital	50	28
Aminothiouracil	——	*
Propylthiouracil	200-400	1.6
Methylthiouracil	200-300	13
Iodothiouracil	200-300	*
Meprocil (methylthiouracil and propylthiouracil)	200-300	*
Tapazole (1-methyl-2-mercaptoimidazole)	20-30	6

*Too few treated to indicate true incidence of reactions.

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LEGENDS

FIG. 1—65-year-old white female.* Symptoms and findings of myxedema.

FIG. 1a—Same woman, 3 months after administration of thyroid, grains 2 daily.

FIG. 2—60-year old white female.** Advanced myxedema.

FIG. 2a—Front and side view to show deposition of myxedematous protein gel within the eyelids.

*Courtesy of Dr. E. J. Feinhandler.

**Courtesy of Dr. Charles Bloom.

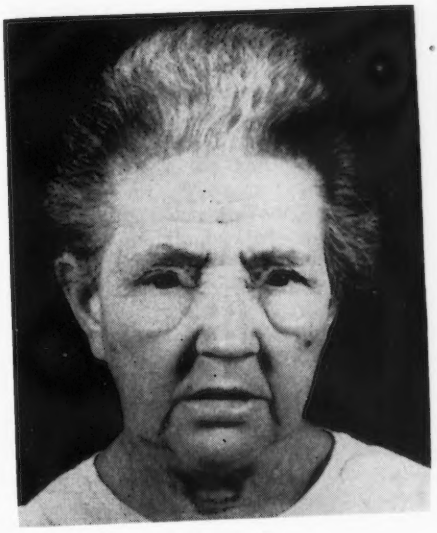

Figure 1

Figure 1A

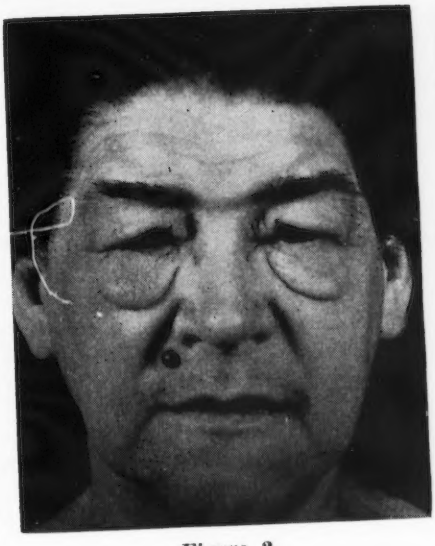

Figure 2

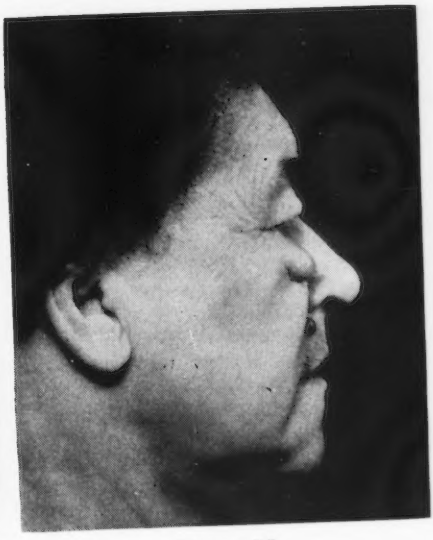

Figure 2A

ROENTGENOSCOPY AND RADIOGRAPHY OF THE ADULT CHEST

JEROME E. STERNS, M.D.*

A precise knowledge of the contents of the thorax is essential at the time of pathological changes and the radiologist is able to offer valuable assistance in aiding the clinician to a definite conclusion when a differential diagnosis is in the offing. It is clearly understood that a chest examination by x-ray means is merely an adjunct to the clinical aspects of a case, the same as the cardiological and pathological laboratories are adjuncts to clinical diagnosis of chest diseases. There is no substitute for a complete history and physical examination and a diagnosis by these means is most important and should precede the referral of a patient for radiological study.

Fluoroscopic examination is an important method for study of the dynamics of respiration and cardiac function in health and disease, and should be done before radiographic study. A logical order should be carried out during fluoroscopic screening. It goes without saying that good dark adaptation is essential and dark-red goggles or glasses should be worn ten to fifteen minutes before beginning fluoroscopy. With this adaptation 70 to 75 KVP and 3 milli-amps are sufficient for viewing. The KVP will vary with the size of the patient and the thickness of the chest. A survey of the thorax is performed to see if the pulmonary fields are clear. The osseous structures are checked for gross abnormalities and the intercostal spaces viewed for narrowing. The costophrenic angles are scanned for the presence of fluid, indicated by obliteration of the sinuses. If pleurisy and effusion are found, the patient should be shifted in position for change in position of the fluid. The extent of the effusion is noted by the fluid level line if one is present, and the thoracic pleural involvement determined by rotating the patient in the oblique and lateral positions. The right anterior oblique is effective for visualizing the more posterior aspects of the right costophrenic gutter and similarly, the left anterior oblique for the left costophrenic sulcus. The diaphragmatic movements are important and should be visualized in early and late inspiration as well as expiration. The normal excursion is approximately ¾ of an inch in moderate inspiration, 1½ to 2 inches with deep breathing, up to 3 inches with forced breathing. Emphysematous patients need more air so the diaphragm will descend to its fullest in early inspiration whereas in the normal the diaphragm descends to its fullest only at the end of deep inspiration. In emphysema the hemidiaphragms are low in position even in expiration and are flattened in contour. The lower ribs flare outward so the thorax is "bell-shaped". Pleuro-diaphragmatic adhesions or an old pleurisy may limit the movement of one or both hemidiaphragms. This may also be true in subphrenic abscess, eventration of the diaphragm, enlarged liver, ascites, pregnancy, and large intra-abdominal tumors. Paradoxical movements should be observed if present as this may mean phrenic paralysis, pleural adhesions, diaphragmatic hernia, or eventration of the diaphragm. If an air bubble is noted above the leaf of the left diaphragm, suspect diaphragmatic hernia; if the leaf of the right diaphragm is involved, interposition of the colon or hernia may be suspected. The diaphragm must be proven to be over the air bubble, as lung cyst and abscess or other cavities can produce similar findings.

As the patient is instructed to slowly inhale and exhale deeply, the pulmonary fields are screened by a narrow transverse slit made by narrowing down the shutters of the fluoroscopic unit. The lung fields are viewed on both sides equally from apices to diaphragmatic levels. Are the lungs illuminated equally on inspiration? Do the lung fields darken equally

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on expiration? The earliest sign of bronchogenic carcinoma may be expiratory emphysema. The tracheobronchial tree expands and lengthens on inspiration, contracts and shortens on expiration. A mainstem bronchial adenoma or carcinoma may allow air to enter the lung but not leave so that an expiratory emphysema is created, noted by failure of one lung to darken during the expiratory movement. In this regard the heart and mediastinum are viewed for shift. If the heart shifts towards the pathological side on inspiration and away from it on expiration, obstructive emphysema is suspected. If the heart moves away from the affected lung on inspiration and towards the lung on expiration, compensatory emphysema is the more likely. In compensatory emphysema the lung is illuminated on inspiration, darkened on expiration. The reverse is true in obstructive emphysema. It should be remembered that both types may be present in the same side of the thorax.

Open the shutters and again scan the lungs. Are any lesions noted? Where? (Obliques and laterals are important for visualizing lesions hidden behind the heart or below the diaphragmatic crests.) Are the lesions calcified or partially calcified; soft in appearance, diffuse and hazy or discrete and dense, or both? Are cavities present? Do they move with respiration? Are the hila in normal position? Do the apices "light-up" on inspiration? These are questions answerable at this time. A dark apex on one or both sides may indicate tuberculosis as well as haziness due to the neck shadow. A shrunken female breast from carcinoma on one side may produce an opacity resembling a lung tumor. Removal of a breast imparts an emphysematous appearance in comparison with the opposite normal side.

The pulmonary markings are important: Are they accentuated in the perihilar areas as in emphysema, congestion, and pneumonitis? Do they descend in dense strands to the bases? These dense strands often signify bronchitis, peribronchitis, and even bronchiectasis. A lipiodol study of the bronchi should be considered. If a lobar or lobular density presents itself, a check for mediastinal shift on inspiration, expiration, or both may help decide for atelectasis or pneumonic infiltration. Notation of narrow intercostal spaces, an elevated diaphragm, and a shift of the mediastinum on the involved side may add up to atelectasis.

The heart and mediastinal structures should be the last aspect of chest roentgenoscopy. Does the superior mediastinum appear widened? If so, is the widening due to aorta or an actual mediastinal mass or glands? This is a favorite area for lymphoblastoma, thymoma, dermoid cysts, metastatic involvement of the hilar lymph nodes, primary malignancy of the lung or esophagus, Boeck's sarcoid, and erythema nodosum. A posteriorly located neurofibroma or tuberculous paravertebral abscess can confuse the picture but rotation into the lateral projection may clarify the location of the mass. Any density or mass should be checked for pulsation, as the widening may be vascular in origin. The trachea is checked for displacement, rechecked by esophageal displacement noted on barium swallow. Causes for tracheal deviation are numerous—atelectasis, substernal thyroid, tuberculosis of the lung and fibrotic traction of the trachea, thymoma, and aneurysm of the arch of the aorta. If the enlarged thyroid is producing the displacement, the swallowing act may exhibit an upward movement of the thyroid gland. Calcification in the mass can give the answer to the nature of the enlargement. In aneurysm of the aortic arch the knob is displaced *upward* and *outward*. Pulsations are more common in an aneurysm. Tuberculosis will have pulmonary changes and a density of fibrosis is noted *toward* the displaced esophogus.

Do the pulmonary arteries reveal widening? Is there evidence of "hilar dance" as in patent ductus arteriosus? The perihilar vascular pattern is accentuated with these findings. The cardiac configuration is noted, whether normal, mitral or aortic in type. Normally the left cardiac border pulsations are more vigorous than on the right, most obvious on the lower left ventricular border noted often

through the gas bubble. Faint auricular pulsation may be noted normally on the right cardiac border, and an increase in intensity to vigorous pulsation when the right ventricle is enlarged. The point of opposite pulsation along the borders is important in detecting early chamber enlargement. The habitus of the individual plays an important role in the shape and position of the heart. The asthenic thorax usually reveals a narrow elongated so-called "hypoplastic" heart. The diaphragm is usually low in position. The sthenic individual possesses the oblique cardiac outline, the configuration described as the normal type of heart. The hypersthenic build produces the aortic or transverse cardiac outline. The heart is not enlarged but is merely transverse due to relatively elevated hemidiaphragms. Scoliosis, pulmonary fibrosis or funnel chest may alter the shape of the heart, producing the mitral configuration.

The common causes of right ventricular enlargement are mitral stenosis and regurgitation, congestive failure, chronic pulmonary disease, pulmonary arteriosclerosis, tricuspid regurgitation and congenital defects. Mitral stenosis and congenital defects (as an interauricular septal defect) produce a small hypolastic aortic knob in the cardiac contour, a prominent pulmonary artery-conus segment and a diminutive left ventricle. The pulmonary arteries are prominent and the perihilar vascular pattern accentuated. The latter findings are more outstanding in IA septal defects. The heart in chronic pulmonary diseases and pulmonary arteriosclerosis is of the oblique type with the addition of an accentuated pulmonary artery-conus segment. On many occasions the fluoroscopist will notice a heart which appears normal except for a mitral configuration. Further examination in the obliques reveals no abnormality such as an enlarged left auricle. In the absence of physical findings on auscultation and no substantiation of a disease process in the past history, the heart should be considered normal. The PA and ROA projections are best to visualize the right ventricle and left auricle. A barium-water mixture is given to the patient to detect esophageal deviation in the left auricular area noted best in the right anterior oblique position. After the patient swallows a spoonful of barium mixture, he is told to inspire deeply and hold his breath. The esophagus is then checked for posterior displacement. Right ventricular enlargement in the ROA produces a prominent pulmonary artery-conus segment while the right ventricle decreases the retrosternal space. In early mitral disease only slight left auricular enlargement may be detected without right ventricular enlargement. Auscultatory findings would be most important to corroborate the roentgenoscopic impression in the earlier phases of rheumatic disease. Pure mitral regurgitation enlarges the left ventricle as well as the left auricle and right ventricle so that the LOA position would enhance recognition of left ventricular enlargement.

Hypertension, peripheral arteriosclerosis, aortic regurgitation and stenosis, coronary arteriosclerosis, nephritis, and coarctation of the aorta cause left ventricular enlargement seen best in the PA and LOA positions where the left ventricular enlargement is noted as a posterior bulge which often fails to clear the vertebral column during rotation of the patient to the left lateral position. It is of considerable importance in aortic regurgitation to note the amplitude of the left ventricular and aortic pulsation. There may be only minimal aortic and ventricular enlargement or even a normal cardia so that the abnormally vigorous pulsation is often the only clue other than the early diastolic murmur on auscultation. This type of pulsation is not seen in hypertension, aortic stenosis, or other diseases that give left ventricular hypertrophy. If the left ventricle is considerably enlarged, the aortic knob is of smaller appearance. The pulsations are less marked when failure occurs and the heart enlarges. If right heart failure ensues, the general cardiac outline may be of the combined aortic and mitral disease.

A small elevation of the left ventricular border is often diagnostic of aneurysm of the cardiac wall, especially if there is feeble to absent contractions of the seg-

ment.

There may be some confusion in the similar appearance of general dilatation of the heart and massive pericardial effusion. The dilated heart retains some semblance of chamber border while in effusion, the borders are indistinct or non-existent. Pulsations are weak in both conditions. It is impossible to detect the apex beat through the effusion. The heart is the so-called "water bottle" type with a narrow vascular pedicle and bulging lateral cardiac contours. Early pericardial effusion is often difficult to detect. 300 cc. to 500 cc. are needed to be visible fluoroscopically. There is filling of the infracardiac recess with a resultant posterior bulge seen best in the lateral view. The fluid then accumulates along the left cardiac border when greater than 500 cc. are present. Constrictive pericarditis, most often caused by tuberculosis and rheumatic fever, is difficult to detect fluoroscopically unless a gross case is present and one finds irregularity of the cardiac border in the form of diminished or absent pulsation, pleural thickening, and limitation of diaphragmatic movements. The cardiac fluoroscopy completes this portion of the roentgen work-up and further study of the patient is by film examination.

Radiographic study of the chest is complimentary to thoracic roentgenoscopy. A permanent record of the roentgenoscopic impression is thus obtained. Many details not evident under the screen are visualized on the film. Radiograms also have the advantage of being either for soft tissue detail or to "see through" a pleural effusion or pulmonary infiltration. The two standard views are the PA and the lateral projections. The obliques with barium swallows are added for cardiac chamber size determination. The PA should be taken with a tube-target-to-patient distance of six feet to minimize distortion (less than 5%). This is also true of the obliques, if taken. A logical order should again be maintained in determining chest pathology — thoracic cage, diaphragm, pulmonary fields, heart and mediastinal structures. The radiologist is aided in arriving at a diagnosis when as much information as possible — history, physical findings, and results of laboratory procedures — is forwarded to him. The diagnostic acumen of the radiologist will no doubt be increased by film interpretation alone, but the patient, referring physician and radiologist alike benefit when there is close cooperation to correlate the clinical and roentgen findings.

As the thoracic cage is examined, deformities, if any, are noted. The osseous architecture and calcium content of the ribs are taken into consideration. At times, multiple myeloma or metastatic malignancy will first make a roentgenological appearance in the rib cage detectable by a defect or punched-out rarefaction. Rib fractures, recent or old, may be noted as evidence of injury, severe bouts of coughing, or even pathological fracture. Cervical ribs may be found. The intercostal spaces are checked on both sides for narrowing. Much the same procedure used in fluoroscopic examination is utilized in the film interpretation. The diaphragm is noted for contour, rib level, elevation of one or both sides, and for the presence of pleurisy, with or without effusion. The pulmonary fields are viewed for possible pathology. The fields are divided vertically into three arbitrary zones. The inner zone contains most of the vascular pattern. The markings feather out in the middle zone and fade in the outer zone. The markings are often seen in the outer zone in acute and chronic chest diseases. Inspiration and expiration films are important in several diseases—emphysema, sub-diaphragmatic abscess, early bronchiogenic carcinoma, foreign body in the bronchus and adhesions. A partial pneumothorax is sometimes seen only in the expiration film.

An important point to remember in film interpretation is the age of the patient. Emphysema or an aortic configuration of the heart, for example, may not cause concern when seen in a patient 60 years of age, but will invoke suspicion of renal, pulmonary, or cardiac pathology if such an abnormality is visualized in a 30 year old patient. Breast shadows have been misinterpreted for pneumonia; the nipples for metastatic invasion; the pectoral musculature for infiltration; the

neck shadows for apical involvement; braids of hair for tuberculosis or malignancy; tumor warts or naevi of the chest wall and particles of clothing for pulmonary nodular infiltration. These are common pitfalls in film reading and remembering these various extraneous items is the best method for avoiding misdiagnosis.

Increased bronchovascular markings will be the most common finding in the pulmonary fields, the causes being numerous for this type of change. If the increased markings are non-specific in type, *i.e.*, follow no typical pattern and are more numerous in the perihilar region and perhaps in the bases, the underlying pathology may be in the upper respiratory tract and the increased vascularity only a physiological change. Tracheobronchitis also gives this finding, but there are pathological changes in the tracheobronchial tree as well. This may also be true in perihilar pneumonias, of viral or bacterial origin. The peribronchial pattern is increased in emphysema, mild cardiac failure, irritating gases, pneumoconiosis, sarcoidosis, abscesses, etc. The pneumonias produce a number of findings in the lung fields. Since the advent of the antibiotics and chemotherapy, the classical lobar pneumonias are rarely seen. The term "pneumonitis" has been attached to most infiltrations inasmuch as the majority of the pneumonic processes have been altered to the point of resembling each other in appearance. The lobular or segmental pneumonias and the peribronchial infiltration forms are probably the most common forms seen. The viral pneumonias mimic the bacterial and may appear as the lobar or lobular forms rather than the perihilar and basilar infiltrations. Subclavicular pneumonias are many times tuberculosis. Pulmonary mycoses (coccidiomycosis, blastomycosis, and actinomycosis) often imitate this phenomenon and bacteriological examination alone will differentiate the underlying pathology. Smaller roughly round infiltrations are sometimes noted in both pulmonary fields and the final diagnosis is often difficult as bronchiolitis, miliary tuberculosis, miliary carcinomatosis, pneumoconiosis, and sarcoidosis can give a similar picture.

The commonest form of reinfection tuberculosis will probably be apical thickening and pulmonary calcification in the apex. Fibrotic strands usually extend to the hilar area representing the lymphatic drainage during the active phase of the disease. The hilus may be retracted towards the apex. Reinfection tuberculosis usually manifests itself in the apical and infraclavicular areas and remains in this location unless spread by the blood stream, bronchi, or breakdown of massive pulmonary involvement. There are various types of tuberculosis, namely 1) exudative form with ill defined, hazy and diffuse densities, 2) productive form producing the more dense, discrete, more sharply defined areas of infiltration, 3) fibrotic and fibroid areas representing healed or healing lesions which are usually seen extending from hilum to apex, 4) caseative form with cavitation and homogeneous density, 5) pneumonic form usually seen in the initial reinfection or in overwhelming tuberculous disease, 6) cavitation, 7) calcification—the form seen in the childhood or primary tuberculosis. Any or all forms may be noted in the same patient. Usually two or more forms are present in the reinfection phase of the disease. As previously mentioned, the pulmonary mycoses can produce a similar picture to tuberculosis.

Calcification in the lungs is usually multiple and varied. The primary complex of tuberculosis is noted by the partially to completely calcified Ghon focus anywhere in the pulmonary fields and calcification of the perihilar lymph nodes. Generalized nodular calcific densities formerly considered to be miliary tuberculosis are now thought to represent histoplasmosis. This can be proven by the histoplasmin test. "Eggshell' calcification of the hilar nodes are sometimes present in the more advanced stages of silicosis. Usually other changes in the lung fields are noted such as fibrosis, nodular densities and fluffy soft appearing infiltrations, if infection or tuberculosis is present concomitantly.

Apical densities and lesions are usually tuberculosis, although pneumonia, su-

perior sulcus tumor, pneumoconiosis, and metastasis, as from hypernephroid carcinoma, can imitate tuberculosis. Rib erosion can sometimes be noted in an over penetrating film if a malignant process is the underlying pathology.

It is difficult to evaluate the bronchovascular markings in clinical bronchitis as increased markings coupled with the findings in emphysema often produce a normal appearance. However, dense strands extending to the bases, particularly with a reticulated or "honeycombed" appearance may indicate bronchiectasis. If the triangle is of pneumonic proportion, suspect superimposed infection or atelectasis. A richer network of vascular basilar pattern may be associated with silicosis or asbestosis.

Atelectasis is important, not for the process itself, but from the viewpoint of etiology. The most common causes are foreign bodies, mucous plugs, bronchogenic carcinoma or adenoma, and bronchial tuberculosis. Various forms of atelectasis are noted. One lobe only may be involved noted by a pneumonic-like process which later becomes fan-like, as the lung shrinks. The lung often retracts totally to the superior or posterior mediastinum so that a displaced fissure toward the atelectasis may be the only indication of an atelectatic proce . Compensatory emphysema is noted in the same lung. If the smaller bronchi are involved by mucous plugs, as for example in bronchial asthma, there is a highly diffuse mottled appearance throughout both pulmonary fields. If a main stem bronchus is occluded, the radiographic findings are striking. There is a marked shift of the heart and mediastinum towards the atelectatic lung. The trachea is deviated with the mediastinum. The diaphragm on the side of the lesion is elevated and the intercostal spaces narrowed. Agenesis of the lung can produce a homogeneous density in one pulmonary field as in atelectasis, but the diaphragm is not elevated, the intercostal spaces are not widened, and the thorax is symmetrical. Bronchographic study will reveal the true identity of the homogenous density.

Pulmonary infarction appears radiographically 12 to 24 hours after initial onset as a hazy infiltration near the lung periphery, with the long border parallel to the pleura. In a day or more, the density becomes well defined. If the infarct is infected, the density can break down and become a typical abscess cavity. The healed infarct may present no visible sequelae or leave a linear scar when resolved. These Fleischman's lines extend horizontally across the lung field to a pleural surface. The lines are also due to segmental atelectasis, interlobar pleurisy, chronic heart failure and following surgical procedures.

Confusion often arises between lung abscess, tuberculous cavity, cavernous neoplasm, interlobar effusion, congenital cyst, and bronchiectasis. Lung abscess is usually in the lower lobes, and often has a fluid level. The wall of the cavity is fairly thick because of surrounding inflammatory changes. A tuberculous cavity is more often in the upper lobes, usually without fluid and containing a fairly thick reaction wall. A single bronchiectatic cavity may give a similar appearance. The congenital cyst is thin walled with little fluid. Bullous emphysema is thin walled without fluid. Compressed lung adjacent to the bulla is noticed if the emphysematous area is large. Bacteriological examination is important for the etiology of cavity formation.

Pulmonary metastases manifest their presence in various ways—a single nodule of varying size, multiple nodules of different diameters, pulmonary nodules with hilar nodal involvement, miliary pulmonary spread, and lymphangitic metastases. The latter type is noted as linear strands of increased density present mainly in the bases and often confused with interstitial fibrosis (from chronic infection, unresolved pneumonia, tuberculosis [more in upper lobes], bronchitis, etc.), Boeck's sarcoid, Hodgkin's disease, lymphosarcoma, leukemias, and post radiation fibrosis. Differentiation may be difficult to impossible at times. Other findings such as enlarged hilar nodes or a known carcinoma elsewhere may help decide the final diagnosis.

Special examination is often indicated

to determine the findings. Laminography or body-section radiography is valuable for revealing thin-walled cavities in tuberculosis or thick-walled cavities in areas of caseation and dense consolidation. Tomography is also useful to separate mediastinal mass from pulmonary arteries, pulmonary cysts, hamartomas, tuberculomas, and carcinomas of the bronchus. Lipiodol study of the main bronchial tree may reveal fusiform, cylindrical or saccular bronchitis. Snub-nosed bronchi filled with lipiodol indicate bronchial asthma. Associated findings as multiple small atelectatic areas of increased density in both lung fields help establish the diagnosis. A bronchogenic carcinoma can be outlined by contrast media.

Examination of the mediastinal structures confirms the fluoroscopic impression—whether the trachea is deviated, whether mediastinal nodes are enlarged or calcified, whether a mass is in the anterior mediastinum (as teratomas and thymomas), middle mediastinum (lymphoblastomas, metastatic and tuberculous nodes) or posterior mediastinum (neurogenic tumors and tuberculous paravertebral abscess). Obliques of the chest will confirm a mass located near the ascending or descending aorta to be an aneurysm as there is no separation of the density from the aorta.

The heart is again the last structure of study in the radiographic survey. The general size and shape are noted. Both obliques and lateral with barium swallows are included for general cardiac chamber determination. The mitral configuration may be produced by mitral stenosis and regurgitation, interauricular septal defect, Lutembacher's syndrome, Eisenmenger complex, and patent ductus arteriosus, although in the latter, the aorta is usually of normal size. The ROA projection serves to outline an enlarged left auricle in mitral stenosis, and together with markedly enlarged pulmonary arteries, Lutembacher's syndrome would be more likely. The type of murmur and history are important, as Eisenmenger complex and Lutembacher's may resemble each other. The small to normal heart does not always mean normality as in tetrology of Fallot the heart appears small to normal in 75% of the cases. The coeur-en-sabot or wooden boot is seen approximately 50% of the time. An elevated apex and small pulmonary arteries are significant. The earliest sign of patent ductus is increased intrapulmonic tension with resultant widened pulmonary arteries. As time elapses, the ventricles enlarge. The larger the patent ductus, the greater the right and left ventricular chamber enlargement. The aorta appears normal. The dancing hila are noted fluoroscopically.

The aortic configuration of the heart is the most common outline encountered in patients. The heart with a slightly enlarged left ventricle and prominent aorta is seen in many conditions previously mentioned and the contour in itself is not significant *per se*. In coarctation, for example, there is left ventricular enlargement but notching of the ribs may be noted, although this is a late finding. In the lateral projection, the aorta fades away as the arch is reached and in itself is significant. The difference in upper and lower extremity pulse pressures further speaks for the presence of coarctation. Aortic regurgitation and aortic stenosis may give similar findings of the typical aortic cardiac outline. Only when failure exists does the left ventricle enlarge to the typical text book description. In older patients, the aortic configuration is altered by pulmonary hypertension, such as chronic lung pathology, so that the contour contains another "bulge", the pulmonary artery. A flattened left cardiac border often signifies myocardial damage or degeneration and one is justified in suggesting such pathology when present. General dilatation of the heart is seen in combined valvular lesions, advanced congestive failure, myocardial weakness, endocrine disturbances, severe or chronic anemias, arterio-venous aneurysms, and congenital lesions. The borders are usually retained in contradistinction to massive pericardial effusion where the chamber borders are indistinct or "lost". Associated pulmonary findings in the form of increased perihilar markings or con-

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A PRELIMINARY STUDY OF THE CHANGES IN SERUM PROTEIN IN DISEASE

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The serum of normal human blood contains a complex mixture of various simple and conjugated proteins. Many of the protein fractions have been separated and demonstrated to be single molecular entities.[1, 2] Electrophoretic, fractionation, ultracentrifugal and certain precipitation technics have been used to demonstrate that changes occur in serum proteins in a large number of pathological conditions. An excellent summary of the results of these studies is to be found in the report by Gutman.[3] From his survey it is apparent that the greatest changes that have been reported are in the relative amounts of each of the constituent proteins. Careful studies using immunological technics have been used to detect minute amounts of proteins in the serums of diseased patients which are not present in normal serums.[4, 5] Using all available technics on the fractionated proteins a number of discrepancies[3] appeared which were explained on the basis that there are qualitative as well as quantitative changes of proteins in disease.

An investigation in this laboratory of the ultraviolet absorption spectra of proteins led to the discovery of a strongly absorbing band which was related to the number of peptide bonds in simple peptides and in proteins. Quantitative studies led to the finding that values of the specific extinction at 2050 Angstroms could be used to interpret the behavior of the band as a whole. It was felt that, with this technic, a rapid method for determining total proteins was made available. Although it is true that practically all other components of serum absorb at about 2050 Angstroms, the large amount of proteins present in serum (in values of gm. per 100 ml.) compared to any other component (in values of mg. per 100 ml.) would make errors relatively small for clinical purposes. An investigation was begun concerning the validity of these considerations which resulted in evidence that indicated rather marked qualitative changes of serum proteins in disease.

Experimental:

The normal serums were those obtained from the blood bank at Mt. Sinai Hospital[6] and were analysed for total proteins by digestion, distillation, and titration. The pathological serums were a random collection of serums from Cook County Hospital which had been analysed for total proteins by digestion and nesslerization.[7]

The serums were diluted 1:3000, 1:4000, 1:5000, and 1:7000 in .005 M Na_2HPO_4 and the optical densities of the diluted solutions were determined, as previously described.[5] The specific extinction (ε, 0.1%) was calculated from the formula, $\varepsilon, 0.1\% = \frac{d}{c}$, where d is the corrected optical density and c is the concentration in gm. per liter.

Dialyses were performed in a refrigerator for 24 hours against 1000 volumes of .005 M Na_2HPO_4.

Results and Discussion:

In figure 1 is given a summary of the results. Each circle or cross represents a determination on a single serum. The circles (normal serums) seem to fall within a well defined area as shown. Three of the "normals," however, have greatly increased values of ε, 0.1% and one has a greatly lowered value of total protein. A check on the abnormality of these latter values was not possible since the specific donors could not be traced. In general the total protein values, except the one noted above, were within the accepted normal range of 6.5-8.2 gm. per 100 ml.[8] The ε, 0.1% value tended to cluster between 31 and 34 with a small

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number of values at about 36 and the larger abnormal values noted above. The crosses (pathological serums) are scattered at generally lower total protein values and larger values of ε, 0.1%. In the square between 7 and 8 gm. protein per 100 ml. and ε, 0.1% between 36 and 38 there appears some overlapping of points.

In spite of the large protein content of serum compared to the other components it was felt that some other strongly absorbing serum component might be sufficiently increased in value so as to account for the marked elevation of ε, 0.1%. A series of samples were displayed and the values determined. In all but one no change was observed within the limit of experimental error. In one case the dialysis resulted in a decrease from a value of 37.9 to 29.6. A seemingly logical explanation for this large fall lies in the well known tendency for some serum proteins to precipitate on dialysis.[3]

This elevation of ε, 0.1% is due preponderantly to some alteration of the qualitative properties of one or several of the component proteins and, to a lesser extent, to an increase in non-protein, high absorbing components.

The qualitative changes in protein absorption, on the basis of studies made earlier, are attributed to

a) a change of amino acid composition of the protein,
b) a stereochemical change of protein configuration resulting in a direct effect on the peptide bond,
c) presence of a new protein having a value of ε, 0.1% greatly in excess of those values for normal serum proteins.[5]

The values of ε, 0.1% for serum albumin (Fraction V) and serum globulin (Fraction II) have been found to be 30.5 and 32.7, respectively.[5] For a normal A/G ratio of about 1.5 there should result, for normal serums, values of the specific absorption about 31.4, if it is assumed that the proteins of serum do not interact so as to affect the absorption of the individual proteins. Most of the values are in excess of this, and, in fact, even exceed the value for globulin. These higher values can be partly explained in terms of the non-protein absorbing materials in serum; on dialysis the fall does not lower ε, 0.1% sufficiently to account for the high reading. It must be recognized that the serum globulin fraction made available to us does not contain all of the globulin fractions. Further it is well recognized that many of the proteins in serum are conjugated with other substances; the methods of fractionation result in the removal of the conjugated material. Some of the discrepancy might be explained on the theory that the conjugated proteins may have higher extinction coefficients than the purified proteins.

This is a preliminary report and the problems indicated above are being investigated further, particularly with a view toward isolating such fractions of proteins as show marked increased values of ε, 0.1%.

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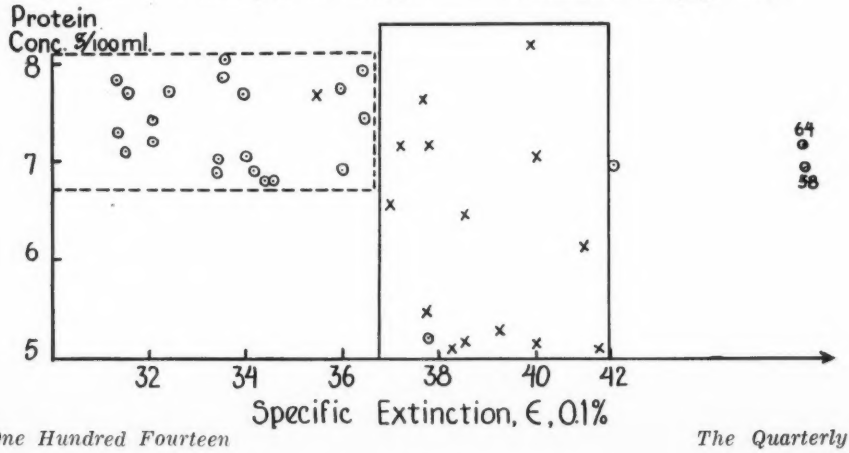

THE NUTRITIONAL APPROACH IN VIRUS RESEARCH

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The introduction of sulfa drugs and antibiotics has opened up a new era in the chemotherapy of infectious diseases. Over the past decade or two, the clinical use of these compounds has yielded such unusually favorable results that physicians and scientists alike have tended to forget the basic reason for their successful application. Briefly this may be stated as follows: Sulfa drugs and antibiotics work because of the differences in the metabolic activities of microbial and mammalian cells. If such differences did not exist, it would not be possible to inflict injury on the one without harming the other. The microbial cell is a unicellular individual capable of performing the chief functions associated with life. It takes in nourishment, excretes waste products, and reproduces its kind. Our aim, in the case of human parasites, is to interfere with these functions. The value of our new chemotherapeutic agents lies in their ability to interrupt certain vital activities of the microbe but not of the mammalian host. The administration of these agents is still largely an empirical matter; they are used because experience has demonstrated their effectiveness *in vitro* and *in vivo* against numerous micro-organisms. Their specific mode of action, on the other hand, is far from understood. This is really not as surprising as it may seem, for in order to obtain such information it would seem necessary first to secure a detailed knowledge of the pathways of cellular assimilations and dissimilations. This has not been possible thus far.

Increasing difficulties are encountered in combating micro-organisms displaying ever higher degrees of parasitism. The less independent an organism is in its metabolic activities, the fewer are the vital links that may be broken or blocked through chemical agents without causing injury to the host. It is for this reason that chemotherapeutic treatment in virus infections has generally met with disappointing results. The only organisms of the rather heterogeneous group of the viruses that have been affected by antibiotics are the largest ones, such as the causative agents of psittacosis and lymphogranuloma venereum. However, it is precisely these organisms whose taxonomic position is much in doubt. In the latest edition of Bergey's Manual of Determinative Bacteriology they are classified in a new genus Miyagawanella, a member of the family Chlamydozoaceae in the order Rickettsiales.

The failure of known antibiotics in the treatment of the majority of virus diseases presents, of course, a great challenge to microbiologists. There are some who persist in the search for antiviral substances in bacteria, molds, actinomycetes, and plants, whereas others are thinking in terms of new avenues of approach. Before discussing these it may be worth while to consider briefly preventative measures of value in the control of virus diseases in order to obtain a more complete picture of the actual needs of the community, on which, after all, the support of future investigative work will depend. Preventative measures may be non-specific or specific. Eradication of Aedes aegypti, the yellow fever mosquito, is a non-specific measure, whereas administration of yellow fever vaccine is a specific measure, employed in the control of the disease. Unfortunately, vaccination is not practiced with success in most virus diseases. Dead viruses are frequently ineffective in stimulating the protective mechanisms of the animal body. What is required are live, attenuated organisms, which are unable to produce the disease but do not differ in antigenic make-up from the virulent ones. This objective has been attained with the mouse-brain adapted 17-D strain of the yellow fever virus and with vaccinia virus. Control of yellow fever and smallpox respectively has also been facilitated because of the uniformity of

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antigenic type of the causative agents. Multiplicity of types would make successful control through vaccination extremely difficult, if not impossible.

Most virus diseases encountered in the population of this country display a relatively mild character. Measles, mumps and chickenpox can be allowed to run their course in most instances. Severe cases can be prevented through the administration of antibodies contained in the serum or, more specifically, the gamma-globulin serum fraction of persons having had the disease. One group of viruses, however, does not fall into this pattern; the neurotropic viruses. Most of these are animal parasites. Man becomes infected only accidentally, either directly as in rabies, or indirectly through an arthropod vector as in virus encephalitis. According to Reeves[1] mainly three specific infections should be considered in the latter group. These are Western and Eastern equine encephalomyelitis and St. Louis encephalitis. These infections are widespread in North America but do not constitute a major public health problem at the present time. Epizootics in horses and occasional outbreaks in man have been recorded. The relative infrequency of occurrence of the clinical diseases appears to be due to unfavorable environmental factors and complicated infection chains. Any future change in the natural balance of these factors may make the diseases much more prevalent in view of the large reservoir of infection in a variety of animals such as birds, mosquitoes, mites and others, in which no signs of illness are manifest. For the immediate present, however, only one specific human infection offers a major challenge to investigators in the field of virus research: poliomyelitis. All the evidence available points to the repiratory tract as the portal of entry of the causative agent. The only effective preventative measure of practical value in respiratory infection is vaccination. Animal experiments have shown that immunization with dead virus preparations fails to produce any protective effect. The search for a live, attenuated, hence harmless vaccine has thus far been unsuccessful. Furthermore, several distinct antigenic types of the virus are known, and their number may be expected to increase with the introduction of improved diagnostic methods.

It is then with particular reference to this infection that new approaches in therapy have been sought. Investigative work with the virus presents many difficulties, mainly due to its pronounced host specificity. Only monkeys can serve as experimental animals for most strains. Rodents are susceptible solely to infection with the Lansing strain. Studies on the effects of nutritional factors in virus infections of animal hosts have been carried out with a variety of organisms. The most one can say about these studies at present is that they offer a few suggestive leads. On the basis of clinical observations and experimental results one tentative generalization seems permissible: viruses thrive best in a well-nourished host, in contrast to bacteria, which are most successful as parasites in an ill-fed host, whose defense mechanisms can be more easily overwhelmed. In poliomyelitis, for example, a direct relationship of incidence to the physical well-being of children has been recognized for some time. Experimental studies on the effect of nutrition on viruses go back several decades. Peyton Rous[2] reported that the development of transmissible chicken sarcoma was checked by illness of the host. Similar responses were observed by Olitzky *et al.*[3] in guinea pigs inoculated with the virus of foot-and-mouth disease, by Rivers[4] in rabbits injected with vaccinia virus, and by others.

A search for specific dietary constituents required for virus multiplication has been conducted by numerous investigators. Foster *et al.*[5], in studies of the Lansing strain of poliomyelitis virus, were able to show that in mice a thiamine deficient diet prolongs the incubation period and reduces the incidence of paralysis and the mortality rate, as compared with control groups on an unrestricted diet. Rasmussen *et al.*[6] confirmed these results with rhesus monkeys. They also noted that after the usual period of observation when essentially all of the well-fed controls had become paralyzed

or had died, if the survivors on the thiamine deficient diet were given liberal amounts of thiamine, some of them came down with typical paralysis. The conclusion was drawn that virus multiplication had not been arrested but that some interference had occurred and altered the course of the disease. Experiments with diets deficient in other vitamins of the B complex have given less clear-cut results.

Lichstein *et al.*[7] studied the effect of single mineral deficiencies on the susceptibility of Swiss mice to Theiler's GDVII virus. A progressively lower incidence of paralysis was obtained by decreasing gradually the amount of potassium and phosphorus in the diet.

In another series of experiments Kearney and his co-workers[8] deleted essential amino acids, one after the other, from an otherwise complete diet. Following inoculation with Theiler's GDVII virus, mice fed a tryptophane deficient diet showed almost no cases of paralysis, whereas close to 100 per cent of the controls were affected. Yet by brain-cord titration it could be demonstrated that the virus had multiplied abundantly in the test animals. Why it failed to produce the clinical signs of the disease could not be explained. It is indeed difficult to visualize in what manner a nutritional deficiency can modify the usual course of an experimental virus infection without affecting survival and reproduction of the causative agent, since it is commonly assumed that the characteristic signs of such an infection are due to the destruction of cellular organization and utilization by the parasite of cellular substance for synthesis of its own constituent desoxyribonucleoprotein (DNP).

While studies on the relation of dietary deficiencies to viral infection have not yielded many tangible results on which to base a comprehensive plan for future research, they have directed attention to a very important fact. Clark[9] states it in these words: "Viruses appear to thrive best under conditions of active tissue metabolism." But what are the conditions of active tissue metabolism? What are the chemical reactions responsible for enhanced cell or tissue activity? It is such questions which have occupied investigators during the last few years. Their studies were not carried out with neurotropic viruses but with bacteriophages. Obviously, the metabolic activities of bacteria can be much better observed and controlled than those of a mammalian host. On the other hand, in view of the wide gulf that separates mammal from bacterium in the evolutionary scale, the worthwhileness of this approach to the problem may be questioned. In its defense it can only be pointed out that there exist certain similarities between the parasites as well as the host cells, which make it appear reasonable to hope that bacteriophage studies might help in elucidating the problem of neurotropic virus infection.

The outstanding characteristic of these viruses is that their parasitism is complete. They do not display any type of metabolic activity but are solely engaged in reproducing their own kind at the expense of the host cells. What then is the mechanism of virus synthesis? What vital part of the cell has to be destroyed in order that virus can be built up? These questions cannot yet be answered in full, but at least a partial explanation of this complicated process has been attempted. Both bacterial cells able to support virus multiplication and nerve cells are rich in ribonucleoprotein (RNP). To obtain high phage titers, bacteria in the logarithmic phase of growth, where their RNP contents is maximal, are added to a phage suspension. Cohen[10] found that infection with phage rapidly reduces cellular RNP. It is noteworthy that the first effect of infection with poliomyelitis virus in the nerve cell is destruction of the characteristic Nissl pattern, which is believed to arise from RNP.

Little is known about the specific role of RNP in cell activities. Caspersson[11] and Brachet[12] have suggested that it is primarily concerned with protein synthesis. Krampitz and Werkman[13] have stated that in bacteria it might constitute the endogenous substrate of the cell. Observations in our laboratory on endogenous respiration, as compared to dissimilation of exogenous nucleotide and ribo-

nucleic acid, lend further support to this assumption. The function of RNP in bacteria might thus be likened to that of glycogen in muscle cells. It is the stored food which is utilized in the process of activity.

Price[14] reported that addition of RNP to a culture of *Staphylococcus muscae* increased the yield of staphylococcal phage. RNP derived from the organism itself as well as from yeast proved equally effective. This finding has not been confirmed with other phages. Recently[15] we encountered a coliphage which was characterized by a preference for old rather than young cells for optimal development. It was also noted that the cells of the host organism had a very high RNP content. This led us to the tentative conclusion that one prerequisite for maximal phage production might be a definite concentration of RNP. This concentration could be expected to vary considerably with the type of phage.

The studies of Cohen[10] on the nutritional aspects of phage multiplication are of particular interest. His investigations, carried out with the B strain of *Escherichia coli* and the much explored tadpole-shaped coliphage T_2, give us a fairly clear picture of the chain of reactions taking place in the infection of a cell with a virus particle. The virus is adsorbed to the cell surface, penetrates into the cell by a mechanism not known at present, and once in the cell, breaks down into numerous smaller particles. It is these particles which begin to direct the host enzymes in the synthesis of material most beneficial to the parasite and of no use to the host itself. During the process of virus multiplication, that is, prior to cellular lysis, the nutritional activities of the cell continue. Food is taken up from the environment, but it is converted into virus DNP by host enzymes obeying the direction of the parasitic invader. Cohen illustrates this process by the shunt in phosphorus utilization. In a normal bacterium 4 P-atoms assimilated from exogenous substrate are divided up between RNP and DNP in the ratio of 3 to 1; in an infected bacterium all 4 are incorporated in virus DNP.

Cohen contended that host RNP did not play any part in virus reproduction but was active only in the synthesis of materials of vital importance to the cell, hence if its own synthesis was inhibited by an infecting virus, cell death became inevitable. To obtain evidence for this contention it was necessary first to determine the origin of ribose and desoxyribose and secondly to demonstrate the effect, if any, of different metabolic pathways on virus synthesis. The dependence of virus synthesis on the substrate available to the host cell is well illustrated in Cohen's studies. There are two ways in which the pentoses, ribose and desoxyribose, can be derived from glucose. Phosphorylated glucose, known as glucose-6-phosphate, can be broken down to a triose phosphate, which may be used by the organism with acetaldehyde to form desoxyribose phosphate. Or, it may first be oxidized to phosphogluconate, which in the process of further oxidation and decarboxylation is converted to ribose phosphate. If gluconate is substituted for glucose as the substrate, only the second pathway is available, and while desoxyribose can be derived from ribose, the amount actually produced is limited. Gluconate was shown to be a poor substrate for virus synthesis. On the other hand, ample amounts of desoxyribose are obtained along the Embden-Meyerhof pathway of glucose dissimilation. It was found to be followed almost exclusively in virus-infected *E. coli* cells.

Another example of a relationship of cellular nutrition to virus multiplication is offered in the work of Ehrlich and Watson[16] and Ehrlich and Knight[17] with a bacteriophage of a lysogenic strain of *Bacillus megatherium*. A lysogenic bacterium can carry on all cellular activities including reproduction with virus formation. Lysogenic *B. megatherium* cells were observed to return to the uninfected state on a glucose nutrient medium, but not on a glucose synthetic medium nor on a nutrient medium without glucose. In explanation of this strange phenomenon, the following hypothesis, supported by additional evidence, was advanced. Desoxyribose can be derived through a degradative pathway from glucose, or through condensation of two and three

carbon compounds. Such compounds may be assumed to arise amply in nutrient peptone and glucose synthetic media as the result of the metabolic activities of the host organism. It must be supposed that the virus is capable of parasitizing this pathway, thus reproducing its own kind. In a glucose nutrient medium, however, most or maybe all desoxyribose will be obtained from the degradation of glucose. Apparently, the virus under study was unable to utilize this pathway and therefore disappeared from the culture.

It is difficult to evaluate the data obtained from experimental studies with a few bacterial viruses. They do not permit of any kind of generalization at this early stage. What is of particular importance in these investigations is that they point in a direction which may well prove fruitful in future research in the virus field. For example, it would be of interest to study the breakdown of carbohydrate by various mammalian tissues in which viruses multiply in order to discover possible differences in the metabolic pathways leading to pentose production. Such a study might yield clues to the problem of the tissue-specificity of viruses. Why should neurotropic viruses, for instance, be unable to parasitize any but nerve cells though they have access to many other parts of the body? Might it not be possible to find a metabolically related tissue to which such viruses could be adapted and thereby deprived of their pathogenicity like the mouse-brain adapted 17-D strain of yellow fever virus? Or, assuming that, as is probable, alternative pathways of carbohydrate dissimilation are discovered in nerve cells, could perhaps chemical means be employed to block at least partly the one most readily parasitized by the invading virus? Only future investigative work can supply answers to these questions.

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Radiography—

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gestion, even edema with the accentuated pattern, add to the general knowledge of the condition of the cardia.

Roentgenological study of the chest, as can be seen, is not a superficial examination but a detailed survey from the bones to the heart. Many conditions often produce similar changes which are clarified only with additional clinical and laboratory findings. It is important to reiterate that only the closest cooperation between clinician and radiologist produces in most instances, a more exact diagnosis.

Proteins—

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A GENERAL CLINICAL APPROACH TO ACYANOTIC CONGENITAL HEART DISEASE

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During the past decade, the field of congenital heart disease has progressed, both in the diagnostic and in the therapeutic aspects, from a sadly neglected, infantile branch of clinical pediatrics and medicine to a well-developed, dynamic specialty. In very few other fields of medicine has so much progress been made in so short a time. Yesterday, the clinician was well thankful to have been able to make the broad diagnosis of congenital heart disease. Today, more and more complex cardiac anomalies are being recognized clinically.

Keeping in step with these diagnostic advances, the field of cardiac surgery has made possible cure or improvement for several types of congenital heart disease and offers promise for correction of still others in the future. In those malformations of the heart not yet amenable to surgical correction, we are nevertheless better able to prognosticate intelligently because of our improved diagnostic ability.

In addition to the tremendous information gained from such diagnostic adjuncts as cardiac catheterization, angiocardiography, unipolar electrocardiography, and more adequate fluoroscopic and roentgenographic examination, much credit for the advancement in this field is due the pathologist who is taking an interest in the subject and is performing more meticulous gross dissection of the heart. In order to recognize many of the anomalies, even at the autopsy table, the pathologist must be thoroughly aware of the various conditions and of their possible variations. Careful clinicopathological correlation has been an integral and vital component in the progress made in the field.

A final and most important factor is our better understanding and more accurate evaluation of the history and physical examination. Indeed, this is the end toward which we strive, at least so far as the clinician is concerned. The importance of the history and physical examination is particularly striking in the group of acyanotic congenital heart diseases. Here we may gain valuable information from such points as the quality and location of the murmur, the intensity of the pulmonic and aortic second sounds, blood pressure readings, and the presence or absence of the femoral pulsations. Such relatively simple observations often may quickly make the diagnosis, which otherwise might be unnecessarily difficult. Indeed, the majority of cardiac anomalies can be diagnosed by an adequate history and careful physical examination, with the aid of a few diagnostic procedures available to most clinicians. The most important of these procedures are unipolar electrocardiography, fluoroscopy, and adequate roentgenographic examination. More extensive procedures, such as angiocardiography and cardiac catheterization, which are expensive, not without danger, and not generally available, are only occasionally absolutely necessary to make the diagnosis with reasonable certainty. Furthermore, one of the ultimate purposes of such procedures is to give us the information which will enable us to diagnose more and more cardiac conditions with a minimum of involved laboratory procedures. It has certainly become more and more obvious that these procedures will not replace our clinical observations but rather will sharpen them.

In a field which has progressed and is continuing to progress so rapidly, it is well to stop for a moment and take account of our advances. Then, from a prac-

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tical standpoint, we can determine how the average clinician is able to apply this recently acquired knowledge. The clinical approach to the group of acyanotic congenital heart diseases offers particularly striking evidence of the diagnostic advances available to all clinicians who are interested in the subject. In addition, the most common of the congenital malformations of the heart fall into this group.

In considering this group clinically, we shall divide the various conditions into two main sub-groups:

I. Those conditions which present themselves in early infancy.

II. Those conditions which present themselves in later childhood. There is obviously much overlapping with such a division. However, since certain conditions must be recognized in early infancy, it is logical to attack the problem in such a way.

I. *Acyanotic Congenital Heart Disease in the Infant*:

Let us first consider the infant who presents the possibility of congenital heart disease for one reason or another, and who is apparently not cyanotic. The usual reasons which bring the attention of the clinician to the possibility of congenital heart disease are one of the following findings or any combination thereof:

1. A murmur.
2. Dyspnea.
3. Apparent cardiac enlargement.

In evaluating such a problem in the absence of cyanosis, one must, of course, first decide whether he is dealing with a congenital cardiac anomaly or with some other condition.

In the first two to three months of life, temporary murmurs of variable intensity are not uncommonly encountered. Practically all of these murmurs will disappear by two to three months of age. The mechanism in the production of such murmurs is not completely understood, but it is felt that they may be related to the normally patent ductus arteriosus and/or foramen ovale or other variations in the dynamics of the infant heart. At any rate, such murmurs do occur and are apparently insignificant. One must, therefore, be extremely cautious in making the diagnosis of congenital heart disease in the first few months of life on the basis of an isolated murmur without other evidence of cardiac abnormality, regardless of the intensity of the murmur. Other findings, such as cardiac hypertrophy or enlargement, unexplained dyspnea, evidence of cardiac decompensation, or hypertension and absent femoral pulsations, must accompany the murmur in order to make the diagnosis with reasonable certainty.

After three months of age, any persistent murmur of grade 3 to 4 intensity is most probably on the basis of congenital heart disease, with or without definite evidence. After two to three years of age, however, rheumatic fever must be excluded as a possible etiologic factor. Rheumatic fever is extremely rare under the age of two years.

It is obvious, therefore, that determination of the presence or absence of cardiac hypertrophy and/or enlargement is of extreme importance. Furthermore, one must be able to differentiate right and left ventricular hypertrophy or preponderance in order to approach the diagnosis in an intelligent fashion. In markedly enlarged hearts, one can usually discover evidence of such enlargement by physical examination. However, one can practically never differentiate right and left ventricular preponderance on the basis of the physical examination alone. In order to confirm cardiac hypertrophy and determine which ventricle is predominantly hypertrophied, one must employ the electrocardiogram, fluoroscopy and roentgenography.

Electrocardiography employing only standard leads is of little or no value in congenital heart disease. One must also employ the unipolar extremity and precordial leads. In addition to chest leads V_1 to V_7, either lead V_3R or V_4R or both should also be utilized. Finally, these should be interpreted by one who is familiar with the infant electrocardiogram which is significantly different from that of the older child or adult.

Roentgenography should consist of at least three views, e.g., PA, RAO, and

LAO. This should be accompanied by fluoroscopy, employing essentially the same views. Such examinations often give a great deal of information in regard to the relative size of both the ventricles and auricles, the pulmonary conus segment, the aorta, and the pulmonary arteries. Fluoroscopy gives additional information about the pulsations of the heart itself as well as the pulmonary vascular pulsations. A barium swallow is particularly useful in giving information about the position of the aorta, the size of the left auricle, and the presence of aberrant vessels.

This combination of electrocardiographic and roentgenographic examination will usually determine the presence of and the localization of cardiac hypertrophy. Occasionally one of the two will be misleading, but careful correlation of the two along with other clinical factors will usually bring out the true facts. In general, the electrocardiogram, with careful interpretation, seems to be the most reliable single procedure in evaluating hypertrophy, especially in those cases which are not accompanied by significant gross enlargments.

Once one has determined the presence of hypertrophy and has localized the predominant ventricle, he has made a big step toward the diagnosis. At least, he has considerably narrowed down the field of possible diagnoses. Before going any further, however, we must first absolutely rule out the presence of latent or subclinical cyanosis. Any degree of latent cyanosis would, of course, radically alter our diagnostic approach.

The lips, mucous membranes, and nailbeds must be carefully inspected, preferably under natural light. This should also be checked while the baby is crying, which will often emphasize a mild cyanosis or bring out a subclinical cyanosis. The red blood count, hemoglobin, and hematocrit should be checked for the presence of some degree of polycythemia, which would be evidence of cyanosis. With such careful clinical evaluation, one can almost always determine the presence of cyanosis. Only rarely, in extremely doubtful cases, is it necessary to determine the arterial oxygen saturation. Indeed, in such cases an oximeter would be a handy apparatus to have available.

At this point, we have determined the following facts:

A. Presence of congenital heart disease.
B. Absence of cyanosis.
C. Presence or absence of cardiac hypertrophy.
D. Localization of hypertrophy — if present.

We can then consider three possible situations:

1. Acyanotic congenital heart disease without evidence of hypertrophy, after three months of age.
2. Acyanotic congenital heart disease with right ventricular hypertrophy or preponderance.
3. Acyanotic congenital heart disease with left ventricular hypertrophy or preponderance.

Let us then consider these different situations in the order listed.

1. An infant is seen after three months of age with a fairly loud murmur and no evidence of cyanosis or cardiac hypertrophy. In such a case, we may consider the following as possible diagnoses:

a. Interventricular septal defect.
b. Interauricular septal defect.
c. Patent ductus arteriosus.
d. Idiopathic dilatation of the pulmonary artery.
e. Isolated pulmonary stenosis.
f. Coarctation of the aorta — adult type.
g. Subaortic stenosis.

These are by far the most common malformations to be considered in this group and include most of the possibilities.

In early infancy, it may be extremely difficult to differentiate many of these conditions. However, most of these malformations present a relatively good prognosis, and it is not imperative to make an absolute diagnosis in the first few months of life. As the child grows older, the various entities become more well-defined. Therefore, careful observation and follow-up is an important part of the diagnosis.

By the age of two to three years, practically every case of patent ductus ar-

teriosus presents a diastolic murmur in addition to the systolic murmur, with a typical, machinery-like quality. Then, the murmur itself will usually make the diagnosis. Without the diastolic component, the diagnosis is extremely difficult in the infant. The electrocardiogram is usually normal. The fluoroscopic findings of a large pulmonary conus, hilar dance, and increased pulsations are similar to those associated with an interauricular septal defect.

A diminished pulmonary second sound and diminished pulmonary pulsations are the outstanding clinical findings in isolated pulmonary stenosis. However, both of these may be difficult to determine in an infant. Eventually, there will be evidence of right ventricular hypertrophy on the electrocardiogram.

Palpation of the femoral pulsations should be a routine part of the physical examination. If this is done, the diagnosis of coarctation of the aorta will probably never be missed. Markedly diminished or absent pulsations will point strongly to the diagnosis of a coarctation. Without evidence of hypertrophy of the heart, within a few months, it is most likely of the adult type. Evidence of relative hypotension in the lower extremities will confirm the diagnosis. The blood pressure in the upper extremities may be normal but is usually at least slightly elevated. As the child grows older, there is eventually evidence of left ventricular preponderance.

The interauricular and interventricular septal defects may be very difficult to distinguish, especially in infancy. A tendancy toward right ventricular preponderance, a history of delayed growth and development, or roentgenographic evidence of a large pulmonary conus with increased pulmonary pulsations are findings more suggestive of an interauricular than of an interventricular defect. The murmurs may be very difficult to differentiate, though the murmur of an interventricular defect is usually louder and heard a little lower down on the chest.

In any patient who is symptom free, with a pulmonic, systolic murmur, a large pulmonary conus segment, and no evidence of cardiac hypertrophy, one must suspect the possibility of idiopathic dilatation of the pulmonary artery. After two to three years of age, this should never be confused with a patent ductus arteriosus because of the typical murmur in the latter condition. In an infant, it also may be difficult to distinguish this condition from an interauricular defect. Fluoroscopic evaluation of the pulmonary pulsations is of extreme importance in such a differential diagnosis. These pulsations are always normal in cases of idiopathic dilatation of the pulmonary artery. The pulmonary second sound is usually of normal intensity, but occasionally seems to be diminished. The condition must then be differentiated from an isolated pulmonary stenosis; again, normal pulmonary vascular pulsations are a very important differential point.

By the age of five to ten years, most of the above conditions can be fairly well differentiated clinically.

2. The infant with evidence already of ventricular hypertrophy presents an entirely different problem. The prognosis is much worse, and the diagnosis must be made very quickly as surgical intervention may be possible in some cases. It is to be emphasized again that the most reliable evidence of early ventricular hypertrophy lies with the electrocardiogram. Unipolar limb and chest leads are absolutely necessary and, if employed, evidence of hypertrophy can usually be recognized. Leads V_1, V_3R, and V_{4R} should always be included. Fluoroscopy is frequently of little or no help.

With acyanotic congenital heart disease and evidence of right ventricular hypertrophy in a young infant, one must consider the following possible diagnoses:

a. Coarctation of the aorta—infantile type.
b. Anomalous pulmonary veins, in which some but not all of the pulmonary veins enter the right auricle.
c. Lutembacher's syndrome (mitral stenosis with an interauricular septal defect).

The most important of these conditions is the infantile coarctation. A method of surgical correction is being contemplated, and therefore, surgical intervention may be possible in the future. Again, palpation of the femoral pulsations and blood pressure determinations are of the utmost importance. Markedly diminished or absent pulsations with absent or low blood pressure in the lower extremities makes the diagnosis. Blood pressure determination in infants is often difficult, so that repeated attempts may have to be made to obtain the pressures. However, this seems to be the only clinical method of establishing the diagnosis. (The width of the cuff should be no greater than two-thirds of the length of the upper arm). Occasionally, there may be cyanosis of the lower extremities, but this is usually not apparent clinically. Arterial oxygen saturation determinations may reveal a difference in the upper and lower extremities. This, of course, would be an important finding if present.

It is practically impossible to diagnose anomalous pulmonary veins clinically without right heart catheterization. It is, nevertheless, important to differentiate this condition from an infantile coarctation.

A Lutembacher's syndrome should be suspected when there is a systolic and an associated diastolic, rumbling murmur over the apex. The second pulmonic sound is very loud and snapping. Fluoroscopy reveals a large right auricle, prominent pulmonary conus area, and markedly accentuated pulmonary vascular pulsations. The diastolic, apical murmur usually gives the first clue.

3. The infant with acyanotic congenital heart disease and evidence of left ventricular hypertrophy brings out the following differential diagnosis:

a. Anomalous left coronary artery, originating from the pulmonary artery. (Bland-White-Garland syndrome).
b. Idiopathic cardiac hypertrophy.
c Marked aortic or subaortic stenosis.

Subaortic or aortic stenosis is only rarely severe enough to cause symptoms or evidence of cardiac hypertrophy in early infancy. The outstanding clinical findings are an aortic, systolic murmur and a diminished or absent second aortic sound. A diminished pulse pressure is also an important sign, but again blood pressures are often difficult to obtain in infants. Also, the normal variations in blood pressure in early infancy are not altogether understood. At any rate, subaortic stenosis is rarely severe enough to cause cardiac hypertrophy in infancy.

Anomalous origin of the left coronary artery and idopathic cardiac hypertrophy are the important diagnostic possibilities in this group. Both may show similar patterns of left ventricular strain on the electrocardiogram and are practically impossible to differentiate clinically. It is hoped that some clinical method of differentiation will be developed since it may be possible to intervene surgically in cases of anomalous left coronary artery. Retrograde aortography may be of value, but as yet is a very dangerous procedure in infants. It is possible, that by producing a surgical aortic-septal defect and thereby increasing the pressure and oxygen concentration in the pulmonary artery, those patients with an anomalous left coronary artery may conceivably be improved to some degree.

II. *The Older Child With Acyanotic Congenital Heart Disease.*

In older children with acyanotic congenital heart disease, the problem is much different than in infants. Many of the previously mentioned conditions are eliminated because of their limited survival time.

1. In the child with no evidence of cardiac hypertrophy, the important conditions to be differentiated are:

a. Interventricular septal defect.
b. Interauricular septal defect.
c. Idiopathic dilatation of the pulmonary artery.
d. Isolated pulmonary stenosis.

The septal defects are often very difficult to differentiate clinically. The presence of a loud, snapping second pulmonic sound, a tendency toward right ventricular preponderance, and a large pulmonary conus segment with increased pulsations on fluoroscopy are points which favor the diagnosis of an inter-

auricular septal defect. However, all of these may be absent, especially in the younger child or in the case of a very small defect. Evidence of delay in growth and development is also suggestive of an interauricular defect if the defect is fairly large. The patient with an isolated interventricular defect usually shows no symptoms and no abnormal cardiac findings. However, a high interventricular defect may be indistinguishable clinically from an interauricular defect.

Idiopathic dilatation of the pulmonary artery is to be suspected in a child with a systolic murmur in the pulmonic area, a large pulmonary conus segment, but definitely no evidence of cardiac hypertrophy. This conditon may be confused with isolated pulmonary stenosis. The differential points are the absent second pulmonic sound, diminished pulmonary pulsations, and the eventual development of right ventricular hypertrophy in most cases of pulmonary stenosis. In the very young child, it may nevertheless be extremely difficult to make the differentiation. Very careful fluoroscopic examination, with special regard to the pulmonary pulsations, is of utmost importance in such cases. Idiopathic pulmonary dilatation occasionally may be confused with an interauricular defect. Here again the character of the second pulmonic sound and the pulmonary pulsations are the important differential points.

2. When there is evidence of right ventricular hypertrophy in the older child, the two most common conditions to consider are isolated pulmonary stenosis and the interauricular septal defect. In most instances, these two can be differentiated fairly easily. A diminished or absent pulmonic second sound and diminished pulmonary vascular pulsations on fluoroscopy are strongly suggestive of an isolated pulmonary stenosis. In marked contradistinction, the interauricular septal defect is characterized by a loud snapping second pulmonic sound and increased pulmonary pulsations. Both conditions usually present a large pulmonary conus segment. Some cases of interauricular and also some cases of interventricular septal defect are accompanied by a relative pulmonary stenosis, as has been demonstrated by right heart catheterization. The cardiac dynamics in such cases are not completely understood, and they are apt to produce a confusing clinical picture which resembles that of an isolated pulmonary stenosis. Very careful fluoroscopic examination is of particular importance here, as the pulmonary pulsations are usually increased. In true pulmonary stenosis, the peripheral pulmonary pulsations are never increased.

Another acyanotic condition which produces right ventricular preponderance is the Lutembacher's syndrome. An apical systolic murmur with a rumbling, diastolic murmur in the same area and a markedly accentuated second pulmonic sound are the outstanding physical findings and are practically always present. Fluoroscopy reveals markedly increased pulmonary pulsations and evidence usually of a very large right auricle, noted in the left oblique view. The electrocardiogram may exhibit very tall, peaked p-waves in addition to definite evidence of right ventricular hypertrophy. The big clue, however, is the diastolic murmur. Such a murmur, along with evidence of a large interauricular defect, makes the diagnosis.

3. Left ventricular hypertrophy in an older, non-cyanotic child is most commonly associated with the following:

a. Patent ductus arteriosus.
b. Coarctation of the aorta, adult type.
c. Subaortic stenosis.

Patent ductus arteriosus can almost always be diagnosed by the characteristic "to-and-fro" machinery murmur. Only rarely should it be confused with other conditions. At any rate, fluoroscopy should easily distinguish the patent ductus from other conditions producing left ventricular hypertrophy. As mentioned previously, there may be no evidence of hypertrophy for a number of years in some cases. Eventually, however, there is at least evidence of left axis deviation.

Coarctation of the aorta should never be overlooked if the femoral pulsations are routinely palpated. The diagnosis is substantiated by determination of blood

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THE USE OF JUDGMENT IN THE TREATMENT OF LEUKEMIA

IRVING A. FRIEDMAN, M.D.*

The diagnosis of leukemia, however accidental, is usually followed by the dreadful solemnity of a poor prognosis, as well as the compulsive urgency to begin treatment. Often, especially in the chronic leukemias, the patient may be very comfortable, have an adequate red blood cell count and hemoglobin level, and have as his only difficulty a "high white count" or an abnormal blood film. The process of treatment with irradiation, radioactive elements, and similar measures is begun in order to bring the "sick white count and differential" back to normal. The course of the patient's disease usually remains unaltered or may even be hastened by these heroic measures. Our experiences at the Anemia Clinic of the Cook County Hospital have led us to the belief that many leukemias and lymphomas, especially of the chronic types, may not require treatment of any kind for long periods of time.

It cannot be too strongly emphasized that one does not treat a diagnosis. The keynote of judicious therapy is meticulous observation of the patient with regard to the appearance of symptoms and signs and the development of anemia. An abnormal white blood cell count is not an indication for therapeutic gymnastics.

The first consideration in the evaluation of the patient is the possibility of a cure. The only conditions in which a cure is possible are Hodgkin's disease and lymphosarcoma, when early recognition makes radical excision of localized tumors, such as lymph nodes and occasionally the spleen, practicable. Since cure is impossible in most cases, treatment is symptomatic and should be directed at systemic manifestations, such as anemia, thrombocytopenia, weakness, fever, excessive perspiration, pruritus, and weight loss, or local manifestations, such as masses which cause pressure or disfigurement. By treating complications as early as they arise, the patient may be carried over years of comfortable living.

The following cases illustrate examples of careful observation and expectant methods of management.

CASE REPORTS

I. Chronic lymphocytic leukemia.

C.M., 59-year-old Negro female, was admitted to the Cook County Hospital on December 6, 1950, with a history of fever, chills, and cough for seven days, and pain in the right hypochondrium for three days. She had been relatively well before this episode.

Physical examination revealed a well-developed, well-nourished patient, not severely ill, with a blood pressure of 130/70, temperature of 101° F., and pulse rate of 100. There were peach-kernel size anterior and posterior cervical lymph nodes as well as small inguinal lymph nodes. On auscultation, the lungs revealed a few rales in the area of the right upper lobe. On abdominal examination, the smooth liver edge was palpable 6 to 8 centimeters and the spleen 3 centimeters below the costal margin.

Initial hemogram showed RBC 2.92, Hgb. 54 per cent, WBC 266,600, polys. 18 per cent, and lymphocytes 82 per cent. The urine revealed 4 plus albumin. Chest films revealed right upper lobe pneumonitis.

The patient improved rapidly with penicillin therapy and was discharged to the Anemia Clinic. In January 1951, she was readmitted for severe follicular tonsillitis associated with severe facial dermatitis and increase in the size of the cervical, submaxillary, and axillary nodes. Because of the dyspnea occur-

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ring with the rapid lymph node enlargement in the neck, she was given x-ray treatments to the neck. These resulted in rapid reduction in the size of the lymph nodes and disappearance of the facial rash. Since then she has had no specific therapy and has been observed periodically in the Anemia Clinic. Her red blood cell count has varied from 4 to 5 million, hemoglobin from 70 to 90 per cent and white blood cell count from 20 to 50 thousand. She has had persistent small cervical nodes, and the spleen has remained 2 to 3 centimeters below the costal margin. The patient has felt exceptionally well and has resumed her usual mode of living.

Comment: This patient's chronic lymphatic leukemia was "discovered" when she developed a severe infection which aggravated her underlying disease. Because of consequent symptoms she required minimal treatment. Barring further complications, she may do well for many years. We feel that our prime obligation is careful observation for further infections and systemic manifestations of her disease. There is no logical rationale for disturbing her homeostasis with periodic therapy simply to try to reduce the number of white blood cells. The treatment in chronic lymphocytic leukemia includes local irradiation for large troublesome nodes, blood transfusions for anemia, and nitrogen mustard, radioactive phosphorus, and steroid therapy for systemic manifestations.

II. Lymphosarcoma.

J. R., 67 year old Negro male, was first seen at the Cook County Hospital in 1944 because of weakness, marked adenopathy in the axillary and inguinal regions, and hepatosplenomegaly. Biopsy of an inguinal node was diagnostic for lymphosarcoma. The ward physician sent him to the x-ray department as an out-patient for treatment to the nodes and spleen. His initial hemogram revealed: Hgb. 85 per cent (13.2 Gm.), RBC 4.62, WBC 8,800, polys 68 per cent, bands 9 per cent, lymphocytes 22 per cent, monocytes 6 per cent, eosinophils 3 per cent, and basophils 1 per cent. In January 1947, he was again admitted for left chest pain which disappeared in 48 hours. At this time his Hgb. was 33 per cent, RBC 3.5, and WBC 3,700. Bone marrow aspiration revealed areas of homogenous infiltration with mature and immature lymphocytes. He was then followed by the Anemia Clinic. During this time he was still getting periodic x-ray therapy but was missing many of his x-ray appointments. Therapy was entirely discontinued in the Fall of 1947 and he was then followed without any specific treatment. During 1948 he felt stronger, his appetite was better, and his physical findings remained about the same. The leukopenia remained between 1800 and 4500 and his hemoglobin stayed between 60 and 75 per cent and RBC around 4 million. His condition remained very good until June 1947, when he was admitted for hematuria. The possible diagnosis of prostatic or bladder involvement with lymphosarcoma was entertained. His condition subsided and he was again followed at the Anemia Clinic and did very well until April 1950, when he experienced exertional dyspnea and leg edema. These symptoms were easily controlled with Mercuhydrin injections and low-salt diet. During 1951 he was hospitalized several times for cardiac failure with good response to cardiac management, but no specific therapy for his lymphosarcoma was required. In January 1952, the patient was admitted to the hospital because of weakness, weight loss and anemia (RBC 2.83 million and 45 per cent hemoglobin). He is to be treated systemically with nitrogen mustard.

Comment: This patient received periodic local x-ray therapy for adenopathy and massive splenomegaly from 1944 to 1947. He actually felt better when x-ray therapy was discontinued and he was not given any specific therapy from 1947 to the present time. Now that systemic manifestations have appeared, treatment is again indicated. Thus, he was given about 4 years of comfortable living during which he was treated only for his cardiac condition which had no relation to his primary disease. Here again, therapy, when indicated, includes local irradiation for troublesome tumors, blood transfusions for anemia, and nitrogen mustard, steroid hormones, or radioac-

tive phosphorous for systemic involvement. Occasionally, splenic irradiation is utilized for marked splenomegaly, and often the systemic symptoms including anemia are alleviated by this treatment. However, there is danger of producing a hemolytic anemia by irradiation of the spleen in this condition, so that the therapist must use this method of treatment cautiously.

III. Chronic myelocytic leukemia.

D. H., 37 year old Negro female, entered the Cook County Hospital on July 25, 1950, with complaints of dizziness, weakness, and pain in the left upper quadrant for six months. There was no weight loss or anorexia.

Physical examination revealed an alert, cooperative, well developed, and well nourished colored female, not acutely ill, with a temperature of 99° F., blood pressure of 130/70, and pulse rate of 88. There were several small lymph nodes (about 1 cm.) in the posterior cervical, axillary, and inguinal regions. The heart and lungs were normal. On abdominal examination the liver was palpated 3 cm. below the right costal margin and the spleen 16 cm. below the left costal margin.

Initial hemogram: Hemoglobin 32 per cent (4.99 Gm.), RBC 2.09, WBC 192,000, polys 38 per cent, bands 11 per cent, eosinophils 1 per cent, basophils 1 per cent, myeloblasts 7 per cent, premyelocytes 9 per cent, myelocytes 14 per cent, metamyelocytes 12 per cent, lymphocytes 3 per cent, 3 nucleated red blood cells per 100 white blood cells, anisocytosis 2 plus, hypochromia one plus, and poikilocytosis one plus. Attempts at marrow aspiration were unsuccessful.

The patent was given Guanozolo from July 24, 1950 until September 29, 1950, during which time there was subjective improvement, consisting of increased strength and appetite, but no objective hematological or clinical changes. Because of severe anemia, the patient was given several blood transfusions. In November 1950, she developed pain in the left upper anterior chest region, and walnut-size purpuric nodules over the arms and legs which were interpreted as leukemic infiltrations. The adenopathy was about the same as before but the spleen enlarged to 19 centimeters below the costal margin and was tender. She was given Urethane (3 grams per day) and has been maintained on this therapy until this time. Two to three months after Urethane was begun her red blood cell count rose to over four million, hemoglobin to 60 and 70 per cent, and the white blood cell count has been between 50 and 130,000. The hemoglobin remained lowered because of severe hemorrhages. The skin infiltrations disappeared, the spleen shrank to about 12 centimeters below the costal margin, and the adenopathy remained the same. The patient is working without difficulty, has gained weight persistently, and has an excellent appetite.

Comment: The results obtained with this patient show what can be done with judicious, minimal therapy. It is noteworthy that she was not treated with x-ray, but with a milder, more conservative therapeutic agent with good results. If treatment is indicated, we always try Urethane first in these patients to avoid the unpleasant effects of radiation. If this is not sufficient, splenic irradiation or radioactive phosphorous may be tried. Blood transfusions are given, as indicated for severe anemia. Here again, treatment is only given to ameliorate symptoms and anemia.

IV. Hodgkin's disease.

M.S., 31 year old white male, was admitted to the Cook County Hospital on April 1, 1947, with a history of having first noted a mass in the right supraclavicular region ten years previously. This mass began to increase in size six to eight months prior to admission. Three weeks before hospitalization he was at another hospital, where biopsy of the mass was reported as Hodgkin's disease. He was advised to come to Cook County Hospital for x-ray therapy.

Physical examination was essentially negative except for a surgical scar at the base of the right side of the neck.

Laboratory findings: RBC 5.24 million, Hgb. 91 per cent, WBC 7,900, and 2 per cent eosinophils on differential count; urinalysis negative; serology negative; NPN 36; chest x-ray negative.

The patient was discharged on April

21, 1947, with no treatment having been given and was referred to the Anemia Clinic for follow-up care. He received a total of 22 x-ray treatments (11 to each side of the neck) between April 23, 1947 and June 25, 1947. He felt well during the period he was followed in Clinic (from April 23, 1947 to August 17, 1951). Repeated examinations failed to show lymphadenopathy, hepatomegaly, or splenomegaly. Red and white blood cell counts were persistently normal with no eosinophilia or monocytosis.

Comment: This case illustrates the benign course that may occur in some cases of Hodgkin's disease. This patient has lived normally and comfortably for 13½ years with minimal local therapy. We might postulate that the local lesion was the solitary site of the disease process and has been removed, with resultant cure. This patient will be observed periodically for the development of local or systemic manifestations of his disease over the years to follow.

DISCUSSION

The effects obtained with these patients illustrate what can be accomplished with careful expectant therapy. It seems rather futile to bombard the patient with unnecessary irradiation of nodes which are not causing difficulty or to give systemic therapy with nitrogen mustard or radioactive elements when the patient is asymptomatic. From our experience, the only result of this type of therapeutic gymnastics is an uncomfortable, unhappy patient, who will have been cheated of his right to live normally with his disease as long as possible. When treatment is indicated, it should be directed to alleviate the complication at hand, using the simplest and safest measure first and resorting to more drastic methods of treatment when they are really needed. A good example of this approach is the management of the patient with chronic myelogenous leukemia in whom Urethane was used despite the very large spleen, with good results, and in whom x-ray therapy was withheld. A goon general rule of therapy in chronic leukemias and lymphomas is to treat localized troublesome tumors with irradiation or early radical excision, if indicated, and to use systemic therapy for the patient exhibiting generalized systemic manifestations of the disease, such as weakness, weight loss, fever, and anemia. In the absence of either local or systemic difficulty, no treatment is indicated.

SUMMARY

The plea is made for the judicious therapy of leukemias, especially of the chronic types. Cases illustrating the method of watchful expectancy and simple management are presented. It is believed that by the use of periodic x-ray or systemic treatment in leukemia and lymphoma, in the absence of troublesome local or systemic symptoms, one is merely treating a diagnosis and adding nothing to the patient's comfort or life expectancy. Meticulous observation of the patient, treating complications as early as they arise, is strongly urged.

Cardiac Disease—

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pressures in the upper and lower extremities. Evidence of collateral circulation may not be present until very late.

In the absence of a machinery murmur, and with good femoral pulsations, aortic or subaortic stenosis is the most probable diagnosis in a non-cyanotic patient with left ventricular hypertrophy. The aortic second sound is usually diminished in these cases, but this finding is often difficult to evaluate in children. It is quite difficult to positively make this diagnosis; one must exclude other conditions which produce left ventricular preponderance.

Comment.

It has not been the purpose of this paper to discuss any of the acyanotic congenital heart malformations in detail, but rather to present a broad, practical approach to the diagnosis of acyanotic congenital heart disease. Only the more common conditions are discussed and only those diagnostic aides which are generally available and safe are considered in the diagnostic evaluation.

CLINICOPATHOLOGIC CONFERENCE

PRESENTED AT MOUNT SINAI HOSPITAL, CHICAGO

DR. I. DAVIDSOHN, Secretary
Abstracted by DR. A. OYAMADA

This patient was a seventeen-year old white male who entered Mount Sinai Hospital for the first time on July 7, 1950, with the complaint of pain in the left hip of three months' duration. The pain was described as a dull ache which began in the left hip and left inguinal region and radiated down the medial aspect of the left thigh to the knee. This pain only occurred when the patient was on his feet. There was no history of swelling, redness, tenderness, or trauma to the hip. General, systemic, and past histories were non-contributory.

On *physical examination*, the patient appeared alert and in no apparent discomfort but was very pale and thin. The chest was thin-walled and clear to auscultation and percussion. The heart had a regular rhythm with no murmurs. The abdomen was thin-walled and scaphoid. No masses or organs were palpated and there were no areas of tenderness. Examination of the upper extremities was negative. Examination of the left hip revealed no erythema and no areas of tenderness. However, on passive flexion of the hip, the patient experienced some pain. He was able to voluntarily abduct, adduct, and extend the hip. However, on flexing the hip, he experienced pain. There were no abnormalities of the left knee or right lower extremity.

On July 17, 1950, the right sacro-iliac joint was opened and a biopsy, curettement, and culture done. The lesion was found to be necrotic and friable. The biopsy revealed fibrous dysplasia and chronic osteomyelitis. The patient was again taken to surgery on July 20th for application of a cast. Another biopsy was taken, which revealed pleomorphic and hyperchromatic nucleated cells. The patient was placed on radiation therapy and post-operatively did well, though he complained of pain intermittently in the left hip.

On August 2nd, the patient spiked a temperature of 102.8° F. orally and complained of weakness and a headache. There was dullness over the left axillary chest at its base with a few inspiratory rales. The patient also complained of tenderness in the scalp. Examination revealed a small nodule over the left parietal region which was non-movable and tender. On August 10th, he complained of pain in the left temporo-mandibular joint on mastication. Examination revealed nothing. The left tympanic membrane and auditory canal were negative. The patient was discharged as improved on August 14, 1950.

2nd Admission: The patient was readmitted to this hospital on October 1, 1950, with complaints of dyspnea and generalized bone pain of several days' duration. Examination at this time revealed a very pale, thin, young white male in acute dyspnea. His temperature was 102.6° F. and pulse 140. There was a large hematoma over the lateral aspect of the left frontal bone. The mouth and tongue were very dry. The trachea was shifted to the left. Examination of the chest revealed dullness to percussion over the anterior and posterior aspects of the right chest with absent breath sounds. The left chest was clear. The apex of the heart was shifted to the left. Rhythm was regular and no murmurs were heard. No organs or masses were palpated on abdominal examination. The extremities were very tender and painful.

The patient's course in the hospital was steadily downhill, with continued dyspnea and disorientation. On October 9, 1950, the interne was called to see the patient. He was breathing very slowly and showed marked air hunger. He expired shortly afterwards.

Discussion of Case

Dr. D. Peckler: This patient had been seen by me since 1946, and was treated on and off for various upper respiratory and middle ear infections. He always was a very thin individual. When I saw him early in 1950 he weighed about 120 pounds and was 5 feet 7 inches tall. The

LABORATORY DATA:

Blood Counts:	RBC	WBC	Hb	C.I.	Stab	Segs	Lymph	Mono	
1st Adm. 7/7/50	4.14	9.0	75%	.91	4	64	26	4	Anisocytosis
" " 7/27/50	4.78	6.6	83%	.87	3	55	32	8	
" " 8/1/50	4.70	6.4	77%	.82	5	76	18	—	
" " 8/2/50		6.4			3	82	10	5	
2nd Adm. 10/1/50	1.54	5.0	23%	.76	12	49	32	5	2 metas

(RBC tend to be microcytic; + + anisocytosis)

Serology: Typhoid "H" — 1:320
Typhoid "O" — 1:80
Para A — 1:160
Par B — 1:80
Undulant fever: Negative

Urinalysis:	React.	Sp.Gr.	WBC	RBC	Alb.	Sugar	Casts
1st Adm. 7/8/50	5.5	1.012	0-1	0	0	0	0
" " 7/17/50	7.0	1.015	0	0	0	0	0
" " 7/21/50	5.5	1.020	0-1	0-2	0	0	0
" " 8/8/50	5.5	1.021	0.1	0	0	0	0
2nd Adm. 10/2/50	5.5	1.018	0-2	0	0	0	0
" " 10/9/50	7.5	1.014	2.4	0	tr.	0	0

Blood Chemistry:	Sugar	Urea N.	Serum Calcium mEq/L	Serum Calcium mg %	Acid Phosphatase	Alk. Phosphatase
1st. Adm. 7/8/50	100	11.5	4.7	9.4	1.2 (N. 0-4)	8.4 (N. 4-12)
" " 8/2/50					2.0 "	8.0 "

Sed. Rate:
1st Adm. 7/10/50 35 Corrected (N. 1-10) Hematocrit—39
Culture from bone for TB: 1st Adm. 7/17/50 — No growth
Transfusions: 1st Adm. 7/12/50 — 250 cc
" " 7/16/50 — 500 cc

history is correct here except for one fact which I discovered very recently. About three months before he came in to see me for this ailment, he had fallen off a bicycle and had hit his back against the fender of a car. His back began to hurt him at that time. As you will notice, the history goes back to about that time. When he came into the office, he could not walk very well, his thigh was at a 45 degree angle to his hip, kept in a flexed position, and the knee was the same way. My impression at that time was that he had tuberculosis of the sacro-iliac joint and he was hospitalized. I did not bother sending him for any x-rays because of the severe pain that he had. He was x-rayed for the first time in the hospital. He got along very well after the radiation therapy, except for the exacerbations of pain in the scalp. He did develop a nodule in the left side of the scalp which was clearly palpable. This was x-rayed. He was sent home ambulatory and got along very well. He came back to the hospital for more x-ray treatments as an Out-Patient. He walked without any evidence of a limp, and you will notice that there is a period of six weeks between his discharge and the time he was readmitted here. About a week before he was readmitted, he became bedridden and he would sleep quite a bit. On awakening he would cry out that he was blind and that he couldn't see. It would take a period of two or three minutes before he regained his visual ability. He complained that he could not hear upon awakening in the morning. His hearing ability would return after a period of three to five minutes. His family was quite upset over the whole situation. We finally hospitalized him on October 1, 1950. His right chest was needled and no fluid was obtained. His course was progressively downhill. He was in oxygen most of the time, getting I.V. fluids, and there was absolutely no change.

Dr. Leo Miller: This case presents several important clinical data of which one should always be cognizant. There are two types of lesions which one must take into consideration. First, this individual presented all the classical signs of a low grade infectious process in the sacro-iliac joint. From the type of individual presented clinically, one would feel that he was dealing with a tuberculous sacro-iliac joint. That was my diagnosis. If one has seen and opened many joints of a tuberculous nature, he will note that they have a musty odor. As we incised

into this joint, we found it encased in purulent material which smelled like a tuberculous joint. We sent that material in for culture and also removed a section of tissue for microscopic study. Of course, the diagnosis was made in the laboratory. The presenting picture should make one think of another lesion which may act similarly—Hodgkin's disease. This has a slow and insidious course, involving the cancellous portion of the bone rather than the joint itself. It shows a reaction with infiltration, as we see in the vertebral column. There have been cases presented showing paravertebral thickening as you see in the x-ray picture of the dorsal vertebrae. As you follow these cases, you find the lesions skipping vertebrae. The diagnosis is that of a Hodgkin's disease and therapy is accordingly instituted. We often see cases like this which are treated periodically for tuberculosis and eventually turn out to be Hodgkin's disease. I think this case is very instructive. In spite of the fact that liquefaction of tissue did occur, and that a musty odor was noted in the Operating Room, the final diagnosis was made on tissue biopsy, which overruled clinical interpretation.

Dr. J. Sterns: We took a film of the pelvis where the patient had the pain. The outstanding finding was sclerosis in the sacro-iliac joint with an area of translucency in it. This sclerosis with apparent necrotic foci of infection within the sclerosis inclined us to agree with the clinical diagnosis of an infectious process. The next film showed a little translucency, which also could be on the basis of infection rather than a malignancy. However, the biopsy came back as an atypical Ewing's tumor. We took some films of the femora and we saw no definite involvement of the shafts. The proximal portion of the shaft is the most favored site of a Ewing's tumor. The lower extremities are most often involved and the next most common regions of involvement are the pelvis, spine, ribs, skull, and jaws. The upper extremities are the least often involved. A chest film was normal. We instituted treatment some time later. However, the treatment was broken off for a time because of the patient. Eventually we finished the treatments which involved a fairly heavy tumor dose to the sacro-iliac joint. We gave 3670 R, which was all the skin could tolerate at that time. The patient did very well, was able to get up and walk (when he first came, he was unable to stand), and did improve markedly. This commonly occurs in Ewing's tumor—the initial lesion clears up with x-ray therapy and the patient then usually comes in three or more years later with generalized metastases. This happens with surgery or x-ray therapy. The prognosis is apparently poor. We took films of the skull when the patient came in with the nodule and found it essentially normal. There were no definite osseous changes. We took a film of the pelvis later and saw a little more sclerosis in this region. There was not much change in the treated area, although clinically the patient was improved. The only other finding was prominence of the left hilum, which may have represented vascular shadow.

Dr. I. Davidsohn: The biopsy received on July 20, 1950, consisted of a fair amount of soft tissue with small particles of bone in it. Microscopic sections revealed granulation and connective tissue separating islands of what appeared to be tumor tissue. (Fig. 1) Under higher magnification were seen spicules of bone, loose connective tissue, and infiltrating tumor, but no normal marrow. (Fig. 2) The tumor presented a fairly monotonous picture with one cell more or less like the other. The tumor cells had large vesicular nuclei and scant amounts of cytoplasm. Within the tumor were areas suggesting rosettes, *i.e.*, collections of cells arranged radially about a space. When these structures were found, three possibilities had to be considered: (1) a metastatic tumor, such as an anaplastic carcinoma or a neuroblastoma; (2) a primary tumor, such as a reticulum cell sarcoma; or (3) a Ewing's tumor, about which I shall have more to say later.

The diagnosis of Ewing's tumor did not impress me as the most likely at first because the location was so atypical. In the diagnosis of tumors of the bone, the pathologist has to rely heavily on the roentgenologist and does well to consult

with him. The pathologist has to be guided by the natural history of tumors. The so-called Ewing's tumor occurs most frequently in the shafts of long bones, although it may occur anywhere. It sometimes is found in bones of the pelvis, but not as frequently as in other locations.

The reticulum stains with silver showed very little reticulum and our slides showed large masses of cells in no particular relation to this reticulum. Therefore reticulum cell sarcoma was excluded. Reticulum cell sarcoma of bone was thoroughly described by Parker and Jackson in 1939. Only two possibilities were left: a metastatic tumor or a Ewing's tumor. We decided that the probable diagnosis was a Ewing's tumor. This was later confirmed at autopsy.

Postmortem Examination

Dr. I. Davidsohn: When the cranial cavity was exposed, the dura was found to be diffusely involved by grayish yellow tumor nodules varying from 3 to 10 mm. in diameter. (Fig. 3) There were also invading nodules in the calvarium, (Fig. 4) measuring 0.5 to 2.5 cm. in diameter, some of them confluent and thus forming larger masses of tumor tissue. The bone was defective in the areas invaded. The largest defect was 3.5x2.5 cm. in the left fronto-parietal region. There was no extension of the tumor into the brain proper. The tumor also infiltrated into the bone of the left supra-orbital ridge and completely surrounded the left optic nerve throughout its course from the optic chiasma. (Fig. 5)

Metastases were found in various other parts of the skeleton, including the ribs, vertebrae, iliac bones, femora, (Fig. 6) and sternum. The vertebrae from T9 to L4 showed the marrow to be largely replaced by grayish yellow tumor, which was soft and fleshy in consistency. The cortex and intervertebral discs were normal. At the level of T9, a well-defined tumor nodule, 2.5 cm. in diameter, bulged from the external surface on section and replaced a portion of the cortex and marrow. In the femur, hyperplastic marrow was replaced grossly in many areas by tumor in addition to diffuse microscopic permeations. The right iliac bone was irregularly but diffusely invaded by grayish yellow tumor, extending into the sacro-iliac joint in one area. This was the area from which the biopsy was removed. Microscopic sections of this tissue were much more like what is expected in a Ewing's tumor—a monotonous picture of round cells with a moderate amount of chromatin, showing numerous mitotic figures, and with an indistinct, scanty cytoplasm. In many places, extensive necrosis was present (Fig. 7). That the necrosis was not due to irradiation therapy could be established by the fact that such necrotic areas were also found in the sternum, where no therapy was administered. Within necrotic areas were seen small abscesses. In some of the necrotic areas of the vertebrae there was granulation tissue and proliferation of fibroblasts, possibly in response to the irradiation therapy. Section of the optic nerve revealed invasion of the surrounding tissue by tumor but no invasion of the nerve itself.

Microscopic study of some lymph nodes demonstrated the presence of scattered tumor cells in the sinusoids in a few areas. As frequently seen in malignant growths, there was participation of the reticulo-endothelial tissue by hyperplasia and by marked erythrophagocytosis. The cause of this erythrophagocytosis would be interesting to study. Transfusions given for this patient's anemia could not be the cause, because the transfusions were given quite a while before death.

The spleen was enlarged, weighing 230 Gms. (N. 120-150 Gm.). The sinusoids were dilated and engorged with blood. The reticulo-endothelial cells were somewhat more prominent than usual and some contained granular brownish pigment or red blood cells. Clumps of tumor cells were present in many of the sinusoids. (Fig. 8) The malpighian follicles appeared normal except for moderately thickened central arterioles.

In the liver, some of the sinusoids contained hyperchromatic mononuclear cells which, on higher magnification, were found to be clumps of tumor cells.

The only other organ where tumor cells were found outside the circulatory system was the pancreas, which disclosed

definite infiltration of the parenchyma by the tumor.

Anatomic Diagnosis:

Ewing's sarcoma of the bones (ilium, vertebrae, ribs, sternum, cranium, and femora) with metastases to the lymph nodes, spleen, liver, pancreas, optic nerve (perineural), dura mater, and skin (scalp). Pathologic fracture of the left femur, bilateral hydrothorax (right 350 cc; left 100 cc). Acute bronchopneumonia and acute passive congestion of the lungs. Acute passive congestion, erythrophagocytosis, and hemochromatosis of the liver and spleen. Reticulo-endothelial hyperplasia and erythrophagocytosis of lymph nodes. Cholesterolosis of the gall bladder. Chronic cystitis of the urinary bladder.

Cause of death: Ewing's sarcoma with multiple metastases.

Summary and Discussion

Dr. Davidsohn: This type of tumor has a relatively recent history. Ewing reported in 1921, before the New York Pathological Society, a series of cases which he took out from the rest of primary tumors of the bone as a separate entity. He did not think it worthwhile to write a separate paper on it, but three years later, in 1924, he again presented some cases before the New York Pathological Society. A few years later the large material of the tumor registry of the American College of Surgeons was reviewed. Among 680 cases were found 40 cases that complied with Ewing's criteria and 10 which were felt to be doubtful cases. The results were presented in two reports.

Myeloma is any tumor originating from the bone marrow. Depending upon the cells which participate as the basic cell in the tumor, one can accept the existence of a variety of myelomas. The most common myeloma is the one known as the plasma cell myeloma, about which there are all kinds of opinions at the present time. Ewing thought that this bone tumor, represented by the case now discussed, was an endothelial myeloma, developing from the endothelium. At the present time there is little doubt in the minds of most people that this is a distinct tumor. There are differences of opinion regarding its genesis. For instance, there are some who say it develops from the reticulum. The origin from the endothelium is questioned because the endothelium is too differentiated to give rise to tumors. The generally accepted conception is that this tumor develops from the reticulum of the bone marrow, the reticulum being an embryonal tissue endowed with many potentialities and which can give rise to all kinds of tumors. If the cell is further differentiated, the result is a plasma cell myeloma. If it is not differentiated, it may give rise to Ewing's sarcoma, as some people call it at the present time. I mentioned previously that, according to the modern conception, the plasma cell is not a real blood cell. In this connection, the idea of the relation of the Ewing's tumor to myeloma is not without interest.

Willis, a prominent British pathologist, in his most stimulating book on tumors, states that the idea about Ewing's sarcoma is completely wrong. He denies the existence of such a tumor. His argument is that in children most cases of so-called Ewing's tumor, on careful autopsy examination, were found to be actually metastatic neuroblastoma. In some cases a small neuroblastoma was discovered hidden in the adrenal or in the vicinity of the adrenal. Other cases, which are not neuroblastomas, are probably metastatic, anaplastic carcinomas or reticulum cell sarcomas. If these cases of neuroblastomas, anaplastic metastatic carcinomas, and reticulum cell sarcomas are taken out, hardly anything remains to constitute a true Ewing's tumor. This is probably an extreme position.

In this country, such authorities on the pathology of bone tumors as Jaffe and Lichtenstein in New York and Bennett in Chicago disagree with Willis and believe he is going too far in eliminating Ewing's tumor, although there is no question that in some cases the diagnosis of Ewing's tumor is being made somewhat too freely. It is sometimes difficult to make the exact diagnosis without an autopsy if one is basing it entirely on surgical material even with the opinion

of the x-ray man. It is true that in some cases one can see what is recognized as a typical x-ray picture of Ewing's tumor. This is the so-called onion-peel type of periosteal reaction. But, even Ewing, in his original report, claimed that this is not as regularly present as some would like us to believe. In other words, there are cases, even where the shaft is involved, where one does not have this type of characteristic x-ray picture.

This tumor occurs mostly in young individuals, in the same age group as osteogenic sarcoma.

The important differentiation between Ewing's sarcoma and osteogenic sarcoma is the fact that the Ewing's tumor does not produce bone. One finds atypical bone production but this is a reactive type of osteoblastic reaction, not an essential part of the tumor. Dr. Peckler mentioned that this boy had a rather delicate bone structure. The importance of this lies in the claim made by some that it is of some help in making a diagnosis of this condition. Osteogenic sarcoma occurs mostly in rather robust children, whereas Ewing's tumor develops in delicate children.

Regarding the relation to the injury which Dr. Peckler mentioned, I think it worthwhile noting, because it has been emphasized, especially by Ewing, that there is frequently a history of an injury. Of course, we are inclined to disregard that and to say that there is no relation between injury and tumor formation—that injury merely brings forth consciousness of trouble, which is then connected with tumor. But who knows?

A statement in the clinical abstract about a high titer of agglutinins against typhoid H & O and paratyphoid is interesting. However, there was a history of some immunization in the National Guard which was followed by pain in the hip. In Ewing's reports, attention was called to the fact that a substantial number of these cases had a history of immunizations against typhoid. Of course, that may not mean very much, but I think it is worthwhile recording that this is another case with a history of immunization. Most of Ewing's material was published in 1921, just after the end of World War I. I wonder whether some of these young people were not immunized in the course of their military service. This may have been merely a coincidence and not a relation of cause and effect.

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LEGENDS

Plate I

Fig. 1. Biopsy of ilium: Ewing's sarcoma (fibrous tissue and islands of tumor). Photomicrograph X120.

Fig. 2. Biopsy of ilium: Ewing's sarcoma. At this higher power magnification the structure of the tumor is found highly cellular. The tumor cells have a large vesicular nucleus and a scant amount of cytoplasm. Photomicrograph X550.

Fig. 3. Dura mater over the brain. These large nodules were metastases of Ewing's sarcoma.

Fig. 4. Inferior aspect of brain with calvarium still attached, showing tumor tissue between the bone and the dura in the regions of the frontal, parietal, and temporal lobes.

Plate II

Fig. 5. Bundles of optic nerve infiltrated and surrounded by tumor cells. Photomicrograph X120.

Fig. 6. Femoral marrow with tumor metastases. Photomicrograph X150.

Fig. 7. Sternum: Area of necrosis within tumor. That the necrosis arose *de novo* is indicated by the fact that no irradiation was given to this area. Photomicrograph X150.

Fig. 8. Spleen: Tumor metastases in sinusoids. Photomicrograph X150.

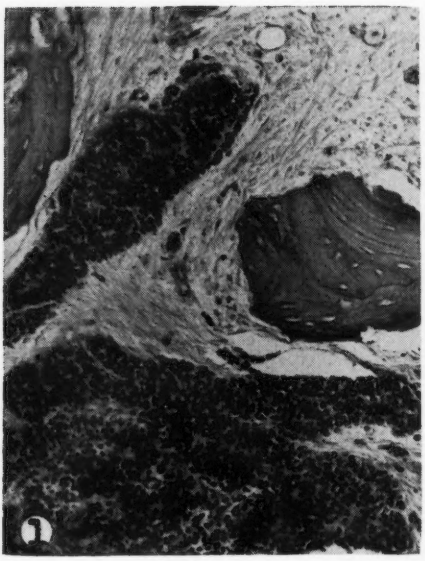

Figure 1

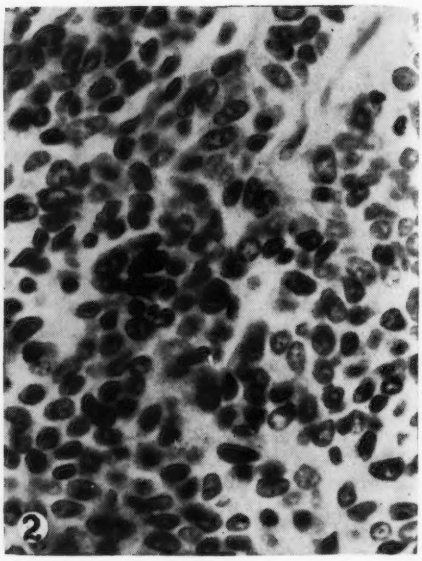

Figure 2

Figure 3

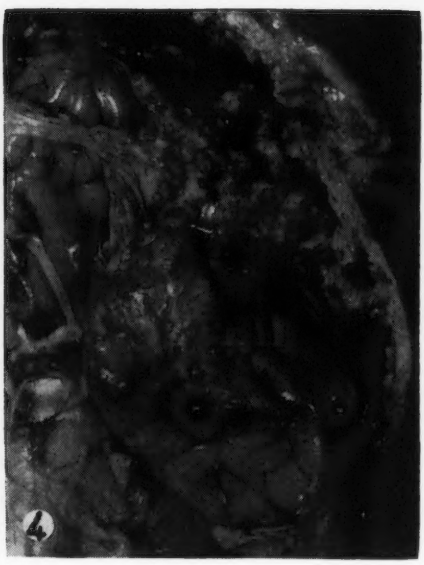

Figure 4

Plate I

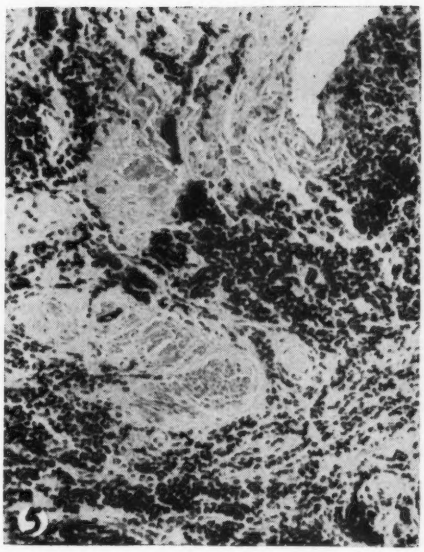

Figure 5

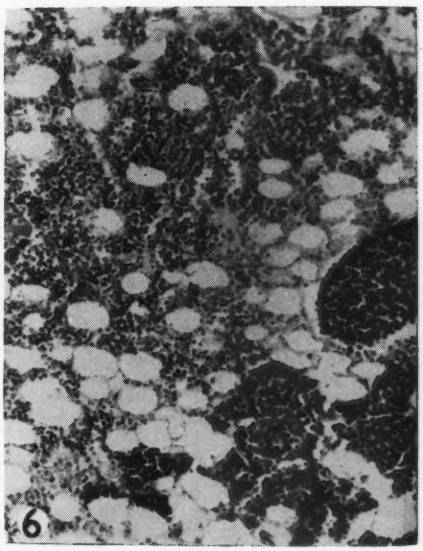

Figure 6

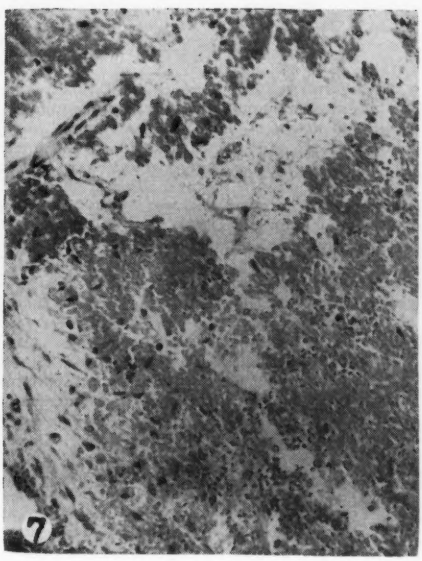

Figure 7

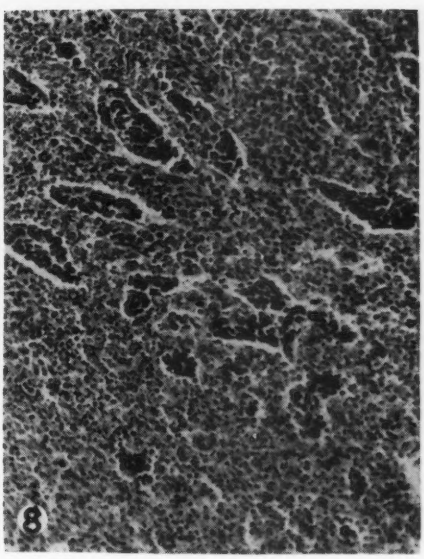

Figure 8

Plate II

BOOK REVIEWS

PLASTIC SURGERY OF THE NOSE by J. B. Brown, M.D. and F. McDowell, M.D. Cloth. First edition. 427 pages with 379 illustrations including 48 in color. St. Louis: C. V. Mosby Company, 1951. $15.00.

This new book is an excellent exposition on practical methods in rhinoplasty. Operative procedures are given in detail and are well illustrated. Two color prints are used advantageously to facilitate an understanding of these procedures. There are numerous photographs of pre- and post-operative cases to clarify the text. The book is well written and carefully organized so that it can serve as a manual for study as well as for reference. Corrections of congenital deformities, war injuries, cysts, tumors and other pathology are thoroughly studied. Careful consideration is given to the physiology of the nose as well as to its appearance. The book is designed specifically for plastic surgeons and is highly recommended to members of this specialty and students of plastic surgery.

TEXTBOOK OF REFRACTION. By Edwin Forbes Tait, M.D., Ph.D. Cloth. 418 pages with 93 figures. Philadelphia and London: W. B. Saunders Company, 1951. $8.00.

Since this text is designed primarily for a student group preparing for practice in the field of ophthalmology, it necessarily covers a voluminous amount of material. This book presupposes for comprehension a fair knowledge of the anatomy and physiology of the eyes and nervous system as well as acquaintance with the principles and methods of geometric and physiologic optics—all of which were covered in the standard medical school courses in optical physiology and in the usual collegiate courses in solid geometry, calculus and physics. The techniques described are easily followed and the equipment described is modern. This book is recommended to all senior medical students and to those practitioners who do refractive procedures. It should be in the medical library of all oculists.

CLINICAL HEMATOLOGY. By Maxwell M. Wintrobe, M.D., Ph.D., Cloth. Third Edition. 1048 pages with 220 illustrations and 17 plates. Philadelphia: Lea and Febiger, 1951. $12.50.

In this third edition, Dr. Wintrobe has continued his style which has made the previous two editions the standard reference text in hematology. Despite this, emphasis is placed on the clinical and practical aspect of this field as well as the theoretical. Most of the laboratory procedures described are intended for routine office practice as well as for the hospital laboratory technician. The presentation of the material is clear and well organized. The bibliography is exceptionally complete. The illustrations are adequate and well drawn. Considerable sections of the text have been completely rewritten—these include the sections on hemolytic anemias, bone marrow, coagulation, the effect of ionizing radiation and hemolytic disease of the newborn. New sections dealing with cytochemistry, splenic puncture and the role of heredity in hemopoietic disorders have been added. Although this text is generally too advanced for the average medical student, it is a necessity for the general practitioner and internist.

PATTERNS OF DISEASE. By Frank L. Apperly, M.D. Cloth. 456 pages with 50 figures and 37 charts. Philadelphia: J. B. Lippincott Company, 1951.

This book attempts to explain disease processes on a basis of pathologic physiology. For each system of the body the author discusses a disease process by tracing its progression through the structural alterations, altered function, the biochemical changes and finally to cure and death. Compensatory mechanisms adopted by the body to neutralize the effects of disease are discussed insofar as present knowledge permits. An attempt is made to explain symptomatology of disease on the basis of manifestations of unaffected tissues and organs in the compensatory scheme. Several charts are of high caliber and would be very valuable from the student's point of view. This book is ideal for sophomore and junior medical students but is not advanced enough or sufficiently complete for the senior or postgraduate student.

THE PHARMACOLOGIC PRINCIPLES OF MEDICAL PRACTICE. By John C. Krantz, Jr., M.D. and C. Jelleff Carr, M.D. Cloth. Second Edition. 1116 pages with 67 tables and 95 figures. Baltimore: The Williams and Wilkins Company, 1951. $10.00.

The central purpose of this text is to "present the pharmacodynamic and pharmacotherapeutic actions of drugs as they are used in the treatment and cure of disease." Because of the rapid advances in pharmacology, extensive revisions had to be made in the text. The chapters on penicillin and streptomycin were condensed into a general chapter on antibiotics to which sections on aureomycin, chloramphenicol and terramycin, in addition to the other antibiotics and chemotherapeutic agents, were added. Two new chapters, one on "The Chemotherapy of Tuberculosis" and another on "The Chemotherapy of Rickettsial Diseases" were included. New chapters on "Anti-motion Sickness Drugs" and "Treatment of the Arthritides: The Adrenal Corticotropic Hormone and Cortisone" have been added. A section on the use of statistics has also been included; this fulfils a need which has long been felt. This book is highly recommended as a textbook in pharmacology for sophomore and junior medical students.

CALLENDER'S SURGICAL ANATOMY. By Barry J. Anson, M.A., Ph.D. (Med. Sc.) and Walter G. Maddock, M.S., M.D., F.A.C.S. Cloth. Third Edition, 1074 pages with 929 illustrations. Philadelphia: W. B. Saunders Company, 1952. $14.00.

In this revised edition of this popular textbook,

it was decided that, "wherever feasible, the original pattern of presentation should be retained". Throughout the book functional anatomy from the surgeon's point of view is stressed. Detailed surgical technic is not presented although general considerations are thoroughly discussed for each surgical disease entity. For example, in discussing diaphragmatic hernia, the section entitled "Surgical Considerations" includes classification, symptomatology, indications for surgical intervention, routes of approach together with beautiful illustrations and diagrams that facilitate comprehension of the textual material. The illustrations are excellent and many of the anatomical plates have been borrowed from the senior author's *Atlas of Human Anatomy*. It is unfortunate that many of the labeled figures still adhere to Latin terminology. The print and binding are superb. This book is a must for all surgeons, surgical residents and advanced students who are learning fundamentals of surgery.

TEXTBOOK OF ORTHOPEDICS by M. B. Howorth, M.D. Cloth First Edition. 1110 pages with 463 illustrations. Philadelphia: W. B. Saunders Company, 1952. $16.00.

"The purpose of this book is to provide the basic facts of the etiology, pathology, diagnosis and treatment of abnormalities and diseases of the musculoskeletal system . . ." Beginning with a history of orthopedics, the first section of the book contains the anatomy and physiology of the musculoskeletal system, a chapter on examination and diagnosis in orthopedics and a final general chapter on treatment. This is followed by a second section subdivided into the various orthodox orthopedic regions and with each subdivision, the various diseases are dealt with separately. The final section is entitled "Neurology in relation to orthopedic surgery" and was written by Fritz Cramer, M.D. This chapter represents a long awaited addition which is absent in most orthopedic textbooks. The text is well written and the illustrations and radiographs are clear and adequately labeled. This book will be useful as a textbook for senior medical students and as a reference work for the general practitioner.

Rx FOR MEDICAL WRITING by Edwin P. Jordan, M.D. and Willard C. Shepard. Cloth. First edition. 112 pages. Philadelphia: W. B. Saunders Company, 1952. $2.50.

With the increase in the volume of medical articles being written, there has been a corresponding increase in the number of books devoted to the improvement of the aforementioned articles. Beginning in the first chapter with the choice of the topic, the authors carry the writer through the various phases of medical journalism. The section on illustrations is especially valuable and can effect a saving of time combined with an increase in their utility if the instructions are followed. The appendix is brief although fairly complete. However, the chapter on statistics is rather short and an increase in its subject matter would be very useful. This book should be in the armamentarium of all physicians who contemplate or are engaged in the writing of scientific articles.

CURRENT THERAPY 1952. Edited by Howard F. Conn, M.D. with a Board of 12 Editorial Consultants. Cloth. 849 pages. Philadelphia: W. B. Saunders Company, 1952. $11.00.

This book, an annual volume, presents the latest approved methods of treatment for the practicing physician. More than 400 diseases are included. The material is not extracted from the current literature but actually represents the therapeutic procedures used in everyday practice by the authority who describes them. Much of the material is simply a repetition of the discussions offered last year; however almost one-half of the treatments are new. Some representative subjects are: Priscoline in pulmonary embolism, cation exchange resins in heart failure, stone solvents in urolithiasis. The text is readable and the binding is of good quality. Every practicing physician who desires the latest information on therapy should add this book to his library.

THE CLINICAL USE OF FLUID AND ELECTROLYTE by John H. Bland, M.D. Cloth. 259 pages. Illustrated. Philadelphia: W. B. Saunders Company, 1952. $6.50.

This book aims "to provide a practical, usable guide to the recognition and treatment of the various fluid and electrolyte abnormalities that may arise in medical and surgical patients." The author has admirably succeeded in his objectives. He has achieved a correlation of established facts in the knowledge of the physiology and chemical pathology of body water and electrolytes with clinical problems as they arise daily at the bedside. In addition to discussing clearly and adequately the rationale behind all forms of modern day fluid and electrolyte therapy, the author has included two superb chapters on fluids and electrolytes in pediatric patients and the aged. The book has a soft cover and is published in manual form. The print is clear and readable. Illustrative charts, and diagrams are liberally interspersed and latest references are included. This book should be studied carefully by residents, interns and all others who are called upon to deal with fluid and electrolyte therapeutic problems in their daily work.

ABSTRACTS SECTION

BLIVAISS, BEN B. Response of Comb and Plumage in Thyroidectomized Brown Leghorn Hens to Hormone Administration. American Journal of Anatomy, *89*, 1951.

The comb of thyroidectomized hens displayed a more marked growth following the simultaneous administration of thyroxin and testosterone than with either alone. This was believed to result from a stimulation by thyroxin of an increase in the utilization and ovarian secretion of androgens.

The amount of thyroxin required to produce the henny feather pattern was proportional to the growth rate of the area in question. The female feather pattern was not produced by the administration of estradiol in doses 30 times larger than those required for its production in the capon or bilaterally ovariectomized poulard. The female plumage pattern appears to result from a synergistic action of thyroid and ovarian secretions.

The dose of thyroxin necessary for an acceleration of feather growth rates to normal levels was proportional to the order of growth rates in normal rather than to the order in thyroidectomized individuals. This may be a consequence of the accelerated ovarian secretion resulting from thyroxin administration. The growth rate pattern of feather areas appears to be influenced by thyroid and ovarian secretions.

DASLER, WALDEMAR, with the technical assistance of CORDES, ELEANOR M. The Effects of Excess Tryptophan and Excess Lysine on the Production of Rickets in the Rat. Journal of Nutrition, Vol. *41*, p. 499 (1950).

Rats receiving the U.S.P. rachitogenic diet No. 2 supplemented with 1% L-lysine monohydrochloride exhibited an increased rate of growth for the first 10 days and a decreased femur ash for the first 20 days of the experiment when compared to control animals receiving no supplement. After 30 days the per cent ash of the femurs of the lysine-fed and the control groups were the same. DL-tryptophane, added to the rachitogenic diet at a level of 1%, gave rise to a decreased rate of growth and an increased femur ash. The growth rate and femur ash of the group of rats receiving both supplements simultaneously did not differ significantly from those of the control animals.

ELIAS, HANS and BENGELSDORF, H. Die Struktur der Lever der Wirbeltiere. Anatomische Nachrichten, Bd. 1, Heft 19/21. Pp. 273-280.

Stereographical and statistical considerations have shown that the classical concept of the vertebrate liver as a net-like tubular gland is untenable.

Instead, the normal vertebrate liver is a continuous mass of cells. The mass is tunneled by the hepatic labyrinth. The latter is composed of the hepatic lacunae. These contain the sinusoids. The walls (liver plates) between neighboring lacunae are one or two cells thick. The liver can be compared with a building. The partitions within this building would be made of solid masonry, the stones representing the liver cells

KOENIG, H.: Differential Extraction of Nucleic Acids from Mammalian Nerve Cells with Perchloric Acid. Journal of The National Cancer Institute, Vol. 10, No. 6, June, 1950.

Ogur et al. (Fed. Proc. 1949, 8:234; Science, 1949, 110; 472) have employed perchloric acid for the selective extraction of ribose nucleic acids and desoxyribose nucleic acids from plant tissues. This is a preliminary report of work underway to apply the foregoing procedure to mammalian nerve cells as a cytochemical technique. Spinal cords of cats and guinea pigs were fixed by vascular perfusion with 10 per cent formalin, cut 10 mu thick and mounted on slides. After deparaffinizing and passage through water, slides were placed in 10 percent perchloric acid for varying periods of time and at several temperatures along with control slides in water. One series of experimental and control slides was stained with thionin at pH 3.24, another with hematoxylin and eosin.

Nerve cells treated with 10 percent perchloric acid at 19.5° C. showed incipient reduction in basophilia of cytoplasm and nucleus at 45 minutes. By 6 hours only traces of basophilia persisted, disappearing by or before 24 hours. Nuclear basophilia of glial, endothelial and ependymal cells progressively diminished though not quite so rapidly. Sections treated with 10 percent perchloric acid at 25° C showed no cytoplasmic basophilia in nerve cells at two hours, and possibly earlier, although glial and other nuclei stained well. Sections stained with hematoxylin and eosin showed no appreciable alterations even when no trace of basophilia remained. This suggests that nucleic acids are removed without influencing cellular morphology and protein structure. This point is being studied further, and work is under way to remove selectively ribonucleic acid at lower temperatures.

SCHOOL NOTES AND NEWS

FACULTY NEWS

President John J. Sheinin has been appointed a member of the Committee on Emergency Medical Service of the Chicago Medical Society and has been appointed Chairman of the Mayor's Committee for inspection of experimental animal quarters in local medical schools and hospitals. Dr. Sheinin has also been elected Fellow of the American Association for the Advancement of Science.

Department of Medicine

Dr. Samuel J. Taub has published a revision of his textbook, "Clinical Allergy."

Dr. Aldo Luisada, Program Director of Cardiology announces the gift of a $2,500 Cambridge electrocardiograph from the Administration of Mount Sinai Hospital to the Laboratory of Cardiology. Dr. Luisada has also received a grant of $5,400 for continuation of studies with gitaligin from the White Laboratories, Inc.

Department of Microbiology and Public Health

Dr. Harold Elishewitz has been appointed collaborator and abstractor for Biological Abstracts, and member of the Abstracting Staff of Excerpta Medica, Section IV. Dr. Elishewitz has also been appointed to the Arrangements and Management Committee of the joint meeting of the American Society of Tropical Medicine, National Malaria Society and American Society of Parasitologists.

Dr. George J. Scheff has been elected a Fellow of the American Association for the Advancement of Science.

Department of Obstetrics and Gynecology

Dr. Irving Siegel has been elected a Fellow of the American College of Surgeons and of the American Academy of Obstetrics and Gynecology.

Department of Ophthalmology

Dr. Paul Hurwitz, Assistant Professor of Ophthalmology, has been granted $2,400 for the study of new drugs in the treatment of the various allergic diseases of the eye by the CIBA Pharmaceutical Products, Inc.

Department of Pathology

Dr. Israel Davidsohn has been elected Vice-President of the Walter Reed Society.

Department of Physiology

Dr. Leonida Santamaria of the University of Perugia, Italy, has arrived at the School for a year of research as a Fulbright Exchange Fellow under the direction of Dr. Piero P. Foa, Professor of Physiology and Pharmacology, on the physiology of the pancreas.

Dr. Piero P. Foa has been elected a Fellow of the American Association for the Advancement of Science.

Department of Surgery

Dr. Philippe Shubik, Assistant Professor of Surgery and Coordinator of the Cancer Teaching Program, and Dr. A. Robert Goldfarb, Associate, Department of Biochemistry, have received a grant of $2,500 from the Atomic Energy Commission for studies of cancer-producing effects of Beta radiation.

The National Cancer Institute has granted $6,000 to Dr. A. C. Ritchie, Research Fellow in Oncology, for studies of factors influencing cancer production in animals.

Dr. Adele Gecht has been certified by the American Board of Surgery.

Department of Urology

Dr. J. S. Grove has been elected Vice-President of The Chicago Urologic Society.

The following faculty appointments and promotions have been announced by President John J. Sheinin:

Department of Gynecology

Dr. Morris W. Rubenstein has been appointed Instructor in Gynecology.

Department of Medicine

Drs. Arthur S. Wagner and Everett G. Weir have been appointed Instructors in Medicine.

The following have been appointed Assistant in Medicine: Dr. Irwin Dvore, Dr. Irving A. Friedman, Dr. Leo M. Goldman, Dr. Milton Hertzberg, Dr. Marvin L. Jaffe (Class of 1950), Dr. Harold E. Klemptner, Dr. Milton M. Ostroff, Dr. William Schwied and Dr. Mitchell Sokoloff.

Department of Microbiology and Public Health

Dr. George J. Scheff has been advanced from Assistant Professor to Associate Professor of Microbiology.

Department of Neurology and Psychiatry

Dr. Louis Schlan has been appointed Instructor in Neurology.

Drs. Klara G. Ranky and Frank F. Evans have been appointed Instructors in Psychiatry.

Dr. Leonard H. Gilman (Class of 1950) has been appointed Assistant in Psychiatry.

Department of Ophthalmology and Otolaryngology

Dr. Hyman S. Green has been appointed Instructor in Ophthalmology.

Drs. David S. Kane and Jack Tresley have been appointed Assistants in Ophthalmology.

Dr. Julius J. Prohovnik has been appointed Instructor in Otolaryngology.

Department of Pediatrics

Dr. Harold X. Gerber has been appointed Instructor in Pediatrics.

Drs. Albert Goldman and Pearl R. Gollin have been appointed Assistants in Pediatrics.

Department of Physiology

Dr. Jay A. Smith has been promoted from Assistant Professor to Associate Professor. (In the last issue of the QUARTERLY it was incorrectly reported that Dr. Smith had been promoted from Associate to Assistant Professor.)

Department of Surgery

Dr. Ellsworth E. Hasbrouck has been appointed Instructor in Surgery.

Drs. Alfred A. Diamond and Eugene A. Noskin have been appointed Assistants in Surgery.

Dr. Herman A. Jacobson has been appointed Associate in Surgery.

ALUMNI NEWS

Class of 1935

Dr. Herbert J. Levine has been elected Chief of Medicine at St. Mary's Hospital, Centralia, Illinois. Dr. Levine has recently published articles in Medical Times and in the Illinois Medical Journal.

Class of 1939

Dr. O. J. Burroughs has recently been elected Secretary-Treasurer of the Staff of St. Mary's Hospital, Centralia, Illinois.

Dr. E. F. Stephens, Jr. has recently been elected Chief of Surgery of St. Mary's Hospital, Centralia, Illinois. Dr. Stephens is also outgoing President of the Marion County Medical Society.

Class of 1940

Dr. Ben H. Barbour, Jr. has been elected Chief of Obstetrics of St. Mary's Hospital, Centralia, Illinois. Dr. Barbour is also outgoing Secretary and Vice President elect of the Marion County Medical Society.

Class of 1944

Dr. Elmer E. Bellinger is now serving as a Captain in the United States Army Medical Corps and is at present stationed in Japan.

Dr. Harold Mosak, also in the United States Army Medical Corps, is now stationed at the U. S. Army Hospital, Fort Hood, Texas.

Class of 1945

Dr. Russell E. Elmer is now a Captain in the Medical Corps, presently stationed at Fort Richardson, Seattle, Washington.

Dr. Jerome Goldflies is now a Captain and Commanding Officer of the 733rd Medical Detachment now stationed in Germany.

Dr. Henry Schnittman has been elected to membership in the American Society of Maxillofacial Surgeons

Congratulations to Dr. and Mrs. Earl Zazove on the birth of their son, Phillip, born September 24, 1951.

Congratulations to Dr. and Mrs. Murray Feldman on the birth of a son, Jerome Ira, on January 17, 1952.

The members of the Faculty, Alumni Association and Students extend their heartfelt sympathy to the families and friends of these honored dead:

Dr. Emanuel M. Kaplan, Assistant Professor of Surgery.

Dr. Paul R. Sowden—Class of 1931.

Dr. Herman Rhoad—Lieutenant Colonel, United States Medical Corps and Commanding Officer at Watertown, New Jersey—Class of 1932.

Class of 1946

The certification of Dr. Leon Love by the American Board of Radiology has recently been announced. Dr. Love announces the opening of his office for the practice of Radiology in New York City.

Congratulations to Dr. and Mrs. Bernard Reizner on the birth of a son, Richard, born September 28, 1951.

Class of 1947

Dr. Myron Saline has been commissioned a Captain and is on active duty with the Army Medical Corps. He is stationed with the 8055th Mobile Army Surgical Headquarters and is doing internal medicine. His unit is the first hospital that has been made mobile, with helicopters to bring in the wounded.

Dr. Jerome Zwanger is spending a month at Oak Ridge, Tennessee, learning isotope procedure.

Congratulations to Dr. and Mrs. Herbert R. Gaines on the birth of their daughter Ellen Barbara on August 21, 1951.

Dr. Edward R. Svetkey is now a Lieutenant in the United States Army Medical Corps and is stationed at the U. S. Army Hospital at Carlisle Barracks, Pennsylvania.

Class of 1949

Dr. Edward Zucker is now stationed in Korea as a member of the United States Army Medical Corps.

Dr. Raymond Firfer his been commissioned a First Lieutenant in the United States Air Force and is stationed at Chanute Field, Illinois.

Class of 1950

Dr. Alfred Greenberg has been appointed Resident in Radiology at the Veterans Administration Hospital at Fort Howard, Maryland.

Congratulations to Dr. and Mrs. Irwin S. Morse, former editor of the QUARTERLY, on the birth of a son, Barry Ira, on October 12, 1951.

Dr. Lawrence Moser is now associated in General Practice with the Roos-hoos Medical Group in California.

ORGANIZATION NEWS

Phi Delta Epsilon

Beta Tau Chapter started its third year at the school with a group of 22 pledges, who were entertained at a smoker at the Illinois Union, attended by Drs. Shabat, Eisenstein, and Phillip Thorek. A "Recognition Dance" followed, in honor of the anniversary of the school's accreditation.

Dr. William Dameshek lectured on "Hypersplenism" in the second John J. Sheinin lecture sponsored as an annual event by the chapter.

The New Year was ushered in by the first in a series of lectures dealing with non-medical subjects. The subject was "The Dilemma of the Modern Novel," and featured a discussion of the writings of Franz Kafka, Ernest Hemingway, and James Faulkner by Stuart Brent. It is planned to have lectures of similar nature become an integral part of the meetings of the chapter.

On February 16, the third annual Tri-chapter Dinner Dance was held at the Furniture Club, with the joint participation of the Illinois and Northwestern chapters and the Graduate Club of Chicago. This event served as the occasion for the initiation of the pledges.

Two fraters achieved distinction on the National Boards this past year. Norman Bacher was ranked on the honor roll (average of 88 or above) nationally for September's preclinical boards, and Burton Krimmer received the top grade in the Physiology board that same month.

Phi Lambda Kappa

The third annual Maurice Oppenheim Lectureship was held at the Kling Auditorium of the Mt. Sinai Hospital on February 6, 1952. The Alpha Rho Chapter was privileged to present one of the foremost cardiologists in the country, Dr. Charles K. Friedberg, of Mt. Sinai Hospital and Columbia University, New York, and the author of "Diseases of the Heart." Dr. Friedberg spoke on the subject "The Etiology, Physiology, Diagnosis, and Treatment of Chronic Cor Pulmonale" before an audience of more than 500 physicians and students. The reception of the lecture by the students and members of the staffs of the school and hospital has pleased all members of this chapter. Favorable comment has been almost universal. Our special thanks to Frater Maurice Laszlo whose efforts made Dr. Friedberg's appearance possible.

On Sunday, February 10, 1952 our annual Induction Dinner was held at the Sheridan Plaza Hotel. At that time 19 new men were inducted including one student from the Loyola School of Medicine whom we hope will reactivate the Gamma Chapter at that school. Our new faculty advisors, Dr. Leroy Levitt and Dr. Joseph Poticha, both attended and addressed the group. About 75 Fraters and Alumni attended the affair which was the most impressive in many years.

Phi Beta Pi

The Beta Mu Chapter has entered the new year in full swing. A stag party was held in January that turned out to be like a good old fashioned get-together. New officers have been elected and plans have been made for a supper-party to be held at the Illini chapter house. Expected guests are faculty members, alumni, and Dr. Leslie Arey (of Northwestern University).

The Phi Beta Pi takes this opportunity to extend its heartiest welcome to the Freshman class and may your stay at Chicago Medical School be a pleasant one. Do not hesitate to call on any of the fraters for assistance.

Student Council

It was with great pride that the Student Council distributed the first edition of The Chicago Medical School Student Directory. With increasing funds it is expected that besides having yearly revisions, the job of printing can be turned over to a professional firm.

Tickets are on sale now for the first school-wide dance. The date is April 19 and the place, the Hamilton Hotel. If the results of ticket sales are favorable, the Council feels that such a dance could be held annually. Whatever profits are realized will be placed in the Oppenheim Memorial Fund.

Four new faces were present at the last Council meeting as the result of elections in the Junior and Freshmen classes. Altchek and Becker are the new representatives for the Freshmen and Mason and Berkowitz for the Juniors.

Because elections have not been held in the Student Council for over a year, the Council decided to hold elections at its last meeting. New officers are:

President: S. Cohn, Senior
Treasurer: R. Langs, Junior
Secretary: M. West, Sophomore

Plans are now under formation for The Medical Center Student Council. It is expected that the problems of the medical student in each school will be discussed along with the actions of the individual councils in solving these problems. It is hoped that some benefit will be derived by the individual schools participating.

Association of Internes and Medical Students

At the 17th Annual convention of the Association of Internes and Medical Students, in December, 1951, the Chicago Medical School chapter was assigned the national leadership of the Committee on Medical Education. The basic job of this committee is to collect, evaluate and disseminate information on new developments in the field of medical education. Special emphasis will be placed on the evaluation of new plans of integration of clinical and pre-clinical studies such as those being attempted at Western Reserve, Yale, and Bowman-Gray.

To aid in stimulating local interest in this work, the CMS chapter will call upon men in the Chicago area to discuss, at open meetings, the current trends in medical education.

Student American Medical Association

The first annual convention of S.A.M.A. was held in Chicago on December 27-28 at the Hotel Sheraton. The meeting was a huge success, and 47 local chapters throughout the country were represented. All proceedings and resolutions were published in the January and February issues of the Journal of the Student American Medical Association.

The new journal is distributed free to all medical students and interns and is published monthly during the regular school year. It contains news of interest to students, as well as articles of scientific and socio-economic importance. Students are being urged to contribute papers for publication.